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Site of nicotine absorption from a vapour inhaler – comparison with cigarette smoking

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Abstract *Objective*: The aim of the study was to assess the site of nicotine absorption during and after use of a nicotine-vapour inhaler compared with that after cigarette smoking.
Methods: Using a catheterisation technique, the nicotine plasma concentration–time profiles in arterial and jugular venous blood after using a nicotine inhaler were compared with those achieved after cigarette smoking a in seven healthy habitual smokers.
Results: After use of the inhaler, arterial nicotine concentrations rose slowly to a maximum level of 5.9 ± 1.5 ng/ml at a mean time to reach peak concentration (t_{max}) of 9.0 ± 1.1 min, whereas jugular venous nicotine levels peaked at 25.4 ± 5.4 ng/ml at 6.7 ± 0.3 min. The concentration–time curves indicate that the absorption occurs mainly via the mucosa of the oral cavity and the pharynx, and that there is minimal absorption via the lungs. In contrast, after smoking a cigarette, arterial nicotine plasma concentrations rose quickly to a maximum level of 49.2 ± 9.7 ng/ml after 4.0 ± 0.6 min, while the maximum concentration of nicotine in the jugular vein was 22.4 ± 3.9 ng/ml after 6.4 ± 0.4 min, indicating primarily pulmonary absorption of nicotine.
Conclusion: Nicotine absorption after use of the vapour inhaler occurs primarily via the mucosa of the oral cavity; the absorption occurs slowly and the arterial nicotine concentration spike, typical of cigarette smoking, is avoided. Thus, the likelihood for abuse of the nicotine inhaler is probably small.

Key words Artery · Jugular vein · Arterio-venous concentration difference

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Introduction

During cigarette smoking, nicotine is rapidly absorbed via the lungs and presented via the arterial circulation to the brain. It is believed that the bolus-like input to the brain elicits massive stimulation of nicotine receptors, thereby activating the dopaminergic reward system, producing pleasurable effects and positive reinforcement and, eventually, resulting in nicotine dependence [1]. The aim of nicotine replacement therapy (NRT) is to avoid the early arterial nicotine concentration spike to prevent the pleasurable effects, yet to alleviate the withdrawal effects by providing a low level source of nicotine. The most commonly used mode of nicotine administration in replacement therapies for smoking cessation are the nicotine chewing gum and the transdermal patch [1].

Recently, a novel nicotine delivery system for NRT was developed – the nicotine-vapour inhaler. It consists of a porous plug loaded with 10 mg nicotine inserted into a plastic cartridge and a mouthpiece. Upon inhalation, gaseous nicotine is released from the plug to the passing air. The inhaler may be used by means of deep inhalations or frequent shallow puffing. Both techniques produce similar steady-state plasma concentrations of nicotine in plasma [2]. The nicotine-vapour inhaler may have advantages over other nicotine preparations, since besides the nicotine replacement, the "puffing" allows behavioural (oral and handling) reinforcement as well as replacement of the conditioned sensory reinforcement associated with the inhalation of cigarette smoke [3]. It was recently shown that the combination of airway sensory replacement with a citric acid inhaler and nicotine replacement with a nicotine patch significantly improved 10-week smoking absti-

nence rates beyond the combination of placebo inhaler and active nicotine patch [4]. The nicotine-vapour inhaler also significantly increased the quit success rate in a number of 1-year placebo-controlled smoking-cessation studies [5, 6, 7, 8].

Previous studies employing nicotine-vapour inhalers have provided indirect evidence, based on the low rate of increase of peripheral venous plasma levels, that a major part of the nicotine inhaled is deposited and absorbed from the oral mucosa [2, 9]. The aim of the present study was to directly assess the site of absorption of nicotine released from the inhaler using catheterisation of a jugular vein, which is a regional vein close to the anticipated site of absorption, and an artery. Our hypothesis was that elevated jugular venous nicotine concentrations preceding the rise of arterial nicotine levels should reflect a major absorption via the oral mucosa. The results for the nicotine-vapour inhaler were compared with those obtained after cigarette smoking.

Subjects and methods

Study design

The study had an open, two-way, single-dose crossover design, including nicotine-vapour inhalation and normal cigarette smoking in habitual smokers. To avoid high baseline nicotine levels subsequent to smoking, the first procedure was the nicotine-vapour inhalation in all sessions, followed after 90 min by smoking. Serial arterial and jugular venous blood samples were taken. The experimental protocol was approved by the institutional human ethics committee at the Karolinska Hospital. All subjects were informed of the nature, purpose and possible risks of the study before consenting to participate.

Subjects

Seven healthy smokers, five males and two females, aged 21–38 years, height 167–192 cm, weight 63–89 kg, were included in the study. The subjects were requested not to smoke or to use any other form of nicotine-containing products for 24 h before the start of the study. Compliance was confirmed by performing expired carbon monoxide (ECO) testing prior to the study start. Carbon monoxide levels were measured utilising a carbon monoxide analyser (Bedfont Micro Smokerlyzer, Bedfont Technical Instruments, Sittingbourne, England). All subjects presented ECO levels less than 10 ppm, indicating abstinence from smoking [10].

Procedure

The subjects arrived at the Department of Clinical Physiology, Karolinska Hospital, at 0800 hours after having had a light breakfast at home. Under local anaesthesia, a catheter was introduced percutaneously into the femoral vein and advanced under fluoroscopic control to the upper vena cava and then positioned so that the tip of the catheter was placed 6–8 cm into the right common jugular vein. A catheter was also inserted into the brachial artery of the non-dominant arm. Arterial and jugular venous blood samples (5 ml) were collected simultaneously from the catheters in sodium-heparinised vacutainers (Venoject, Terumo Medical Corp., Somerset, N.J.) before, during and at timed intervals after nicotine administration, as indicated in Fig. 1. The blood samples were centrifuged at 1000 *g* for 10 min at +4 °C, and plasma was transferred to cryo-tubes within 60 min and frozen (−80 °C). Heart rate and blood pressure, measured from the electrocardiogram and with a sphygmomanometer, respectively, were monitored before, during and at 30 min after each administration.

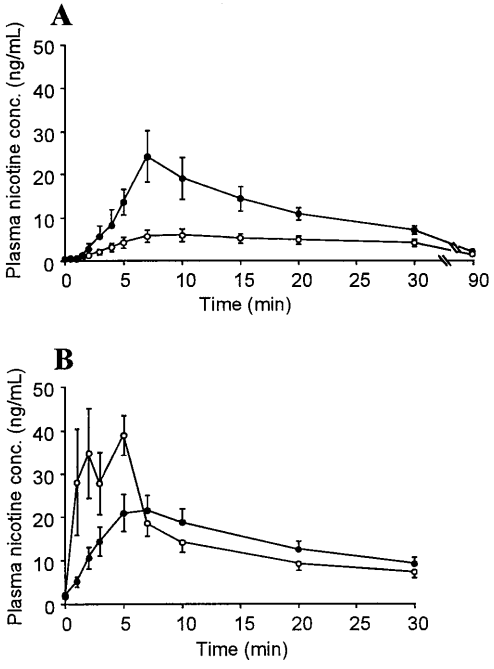

Fig. 1 **A** Mean ± SEM arterial (○) and jugular venous (●) nicotine concentrations after using one inhaler for 5 min ($n = 7$). **B** Mean ± SEM arterial (○) and jugular venous (●) nicotine concentrations after smoking one cigarette over 5 min ($n = 7$). Please note that the arteriovenous difference is reversed for the inhaler relative to the cigarette

Nicotine administration

A nicotine-vapour inhaler (Pharmacia and Upjohn, Helsingborg, Sweden), containing a porous plug impregnated with 10 mg of nicotine + 1 mg menthol, was used in the studies. The subjects made a deep inhalation over a 5-s period, four times per minute for a total of 5 min (20 inhalations). The average nicotine yield in the present study was estimated to be approximately 1.1 mg [2]. The subjects were trained in the use of the inhalers for at least 1 week before the study day. Ninety minutes after the end of the inhalations, the subjects were requested to smoke one cigarette of the Swedish brand "Blend Gul", average yield 0.9 mg nicotine/cigarette, with approximately four puffs per min during a 5-min period with as equally spaced puffs as possible.

Analysis

Nicotine plasma concentrations were determined in duplicate by means of capillary gas chromatography with a nitrogen-selective detector after single-step liquid–liquid extraction of the plasma sample [2]. The plasma sample was mixed with 5 M sodium hydroxide and extracted into 1% *n*-butanol in toluene. The sample extract was injected onto a capillary gas chromatographic system equipped with a fused silicia capillary column coated with 95% dimethyl-, 5% phenyl-silicone (CP-Sil 8CB, Chrompack, Middleburg, The Netherlands). Helium was used as the carrier gas and *N*-methylanabasine was used as an internal standard. The nicotine concentrations were determined from a four-point standard curve,

and the limit of quantitation was 0.5 ng/ml. The coefficient of variation was less than 4% above the 5-ng/ml level.

Statistical methods

Standard statistical methods were employed. Results are presented as mean ± SEM.

Results

Nicotine plasma concentrations after use of the inhaler

The nicotine concentrations in arterial and jugular venous plasma are depicted in Fig. 1. During and after use of the inhaler, the mean arterial nicotine plasma concentrations rose gradually to a peak (C_{max}) of 5.8 ± 1.5 ng/ml obtained 10 min (t_{max}) after start of inhalation. The mean individual C_{max} value was 5.9 ± 1.5 ng/ml (range 2.0–12.6 ng/ml) achieved at a mean t_{max} of 9.0 ± 1.1 min (range 7–15 min). This level was maintained for up to 20–30 min after the start of inhalation. The mean area under the plasma concentration–time curve $(AUC)_{0-45}$ for the arterial nicotine concentrations was 189 ± 40 ng/ml/min. The mean jugular vein nicotine plasma concentrations increased to a peak of 24.1 ± 6.0 ng/ml obtained at 7 min after the start of inhalation. A mean individual C_{max} value of 25.4 ± 5.4 ng/ml (range 7.3–47.3 ng/ml) was achieved at a mean t_{max} of 6.7 ± 0.3 min (range 5–7 min) after the start of inhalation. The jugular venous nicotine concentration exceeded that of the artery at all time points of the study (Fig. 1A).

Nicotine concentrations following smoking of a cigarette

The mean arterial nicotine plasma concentrations increased rapidly during smoking of the cigarette and it reached a peak of 38.9 ± 4.7 ng/ml at 5 min after the start of smoking (Fig. 1B). The mean individual C_{max} value was 49.2 ± 9.7 ng/ml (range 22.5–99.3 ng/ml) achieved at a mean t_{max} of 4.0 ± 0.6 min (range 1–5 min). From this time point, the arterial nicotine concentration decreased rapidly during the remaining study period. The mean arterial concentration AUC_{0-45} was 543 ± 93 ng/ml/min, approximately three times greater than the corresponding value following use of the inhaler ($P < 0.001$). The mean jugular venous nicotine plasma concentrations increased to a peak of 21.6 ± 3.5 ng/ml obtained at 7 min after the start of smoking the cigarette. The mean individual C_{max} value was 22.4 ± 3.9 ng/ml (range 6.7–36.6 ng/ml) achieved at a mean t_{max} of 6.4 ± 0.4 min (range 5–7 min). The initial rise in arterial nicotine concentration during smoking exceeded the rise in jugular venous concentration, but at approximately 2 min after cessation of smoking the arterial concentration became lower than the jugular venous level (Fig. 1B).

Heart rate and blood pressure

The basal heart rate was 67 ± 5 beats/minute (bpm) and systolic and diastolic blood pressure amounted to 117/76 mmHg. There was an average increase in heart rate of 7 ± 3 bpm at 5 min after the first inhalation from the vapour inhaler, while blood pressure remained constant. During smoking of the cigarette, heart rate increased 15 ± 5 bpm, but no change in blood pressure was observed.

Adverse effects

Three subjects experienced mild to moderate dizziness after smoking the cigarette. One subject also reported nausea, and one subject experienced transient anxiety. No other adverse effects were reported when using the inhaler.

Discussion

The primary finding of the present study is that a major proportion of the nicotine absorption after use of the nicotine-vapour inhaler occurs from the oral mucosa rather than from the lungs. Using an intravascular catheterisation technique, it was possible to monitor the nicotine concentration–time curves in arterial and jugular venous plasma samples. Since the jugular venous nicotine concentration markedly exceeded the arterial concentration both during and for more than 30 min after use of the inhaler (Fig. 1A), nearly all of the nicotine absorbed to the circulation must derive from the oral cavity and the pharynx. This resulted in relatively slow nicotine absorption and a modest and gradual rise in the arterial nicotine concentration to peak levels of approximately 6 ng/ml. It should be mentioned, however, that exact quantitative calculations cannot be made since blood flow in the jugular region was not measured. The present observations are in good agreement with the findings of recent studies employing positron emission tomography (PET) technique and inhalations of ^{11}C-nicotine from a vapour inhaler [11, 12]. Approximately 45% of the radioactivity (^{11}C-nicotine) released was recovered in the oral cavity and only 5% or less was found in the lungs. Most previous studies of the disposition of nicotine were based on peripheral venous blood concentration–time curves after nicotine administration, although it has been shown that arterial plasma levels of nicotine after smoking a cigarette may be ten times higher than the peripheral venous levels [13]. The low rate of increase of peripheral venous nicotine levels following the use of a nicotine-

vapour inhaler have been taken to indicate that a major part of the nicotine inhaled was deposited in the mouth [2, 9]. The most likely explanation for the large deposition of nicotine in the upper airways is its high water solubility [14].

In contrast to the findings for the nicotine inhaler, cigarette smoking was accompanied by a rapid and early rise in arterial nicotine concentration (Fig. 1B) [13, 15]. The peak arterial nicotine concentrations of approximately 20–100 ng/ml during smoking are in agreement with previous reports [13, 15, 16, 17]. Since blood sampling was not co-ordinated with puffing on the cigarette, there was considerable variability in arterial nicotine levels during smoking, but the concentrations consistently exceeded those in the jugular venous samples in all subjects. The findings indicate that, during cigarette smoking, nicotine absorption occurred from regions other than the drainage area of the jugular vein. The rapidity and magnitude of the rise in concentration are consistent with pulmonary absorption of nicotine during cigarette smoking. Again, it should be emphasised, the data do not allow quantitative calculations, and a small proportion of nicotine absorption from the oral mucosa and the upper airways during cigarette smoking cannot be excluded. However, the finding of a lower arterial than jugular venous nicotine concentration after the end of the smoking period (Fig. 1B) should be viewed as a consequence of the non-steady-state situation and the longer mean circulation time for the jugular venous region, rather than indicating oral absorption of nicotine.

Recently, results regarding a nicotine nasal spray have been reported [15]. The arterial nicotine t_{max} for the nasal spray was reached after 5 min compared with 9 min when using the nicotine inhaler. The difference between arterial t_{max} for nicotine after use of the nasal spray or inhaler, respectively, may be due to dissimilarities in the nature and vascularisation of the epithelium of the nasal and oral cavities. From the nasal cavity, nicotine is absorbed through a loose epithelium into a rich submucosal venous plexus, while, from the oral cavity, the absorption is through a tighter, less vascularised mucosa. The results thus demonstrate the differing pharmacokinetic profiles of the nasal spray and the inhaler, due to their different sites of absorption.

The pharmacokinetic profile of a reinforcing drug is considered a contributing factor to abuse [18]. Cigarette smoking with its bolus-like input to the brain is regarded as the most reinforcing and dependence-producing form of nicotine administration [18]. Significant plasma concentrations of nicotine have been demonstrated as quickly as 1 min after the start of inhalation of cigarette smoke [17]. The pulmonary absorption of nicotine during cigarette smoking is facilitated by a large alveolar surface area, thin alveolar endothelial layers, an extensive capillary bed and a large blood flow. Nicotine is thus absorbed rapidly from the lungs and it has been suggested that nicotine delivery to the brain after cigarette smoking is even more rapid than after intravenous infusion of nicotine [1]. In the present study, minimal, if any, pulmonary absorption of nicotine from the vapour inhaler was observed. Thus, it is likely that the inhaler has a low abuse potential. This is also supported by results of several clinical trials [5, 6, 7, 8]. In addition, blood nicotine levels produced with the inhaler under "real-life" conditions were lower than those seen in chronic cigarette smokers, approximately 30% of smoking levels [19].

In conclusion, our results indicate a slow, gradual nicotine absorption predominantly via the mucosa of the oral cavity after use of the nicotine inhaler. Thereby, the arterial nicotine concentration spike typical of cigarette smoking is avoided. The airway sensory reinforcement provides an opportunity for therapy of a conditioned behaviour, while the likelihood of abuse of the nicotine inhaler should be no greater than that for the nicotine-containing chewing gum.

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