

Preliminary Analysis of Blood Nicotine Concentration from Intellicig® NDD

1.0 Aim

To determine the bioavailability and C_{max} (the maximum concentration) of Nicotine from ECOpure preparations using an Intellicig® Nicotine Delivery Device (NDD).

2.0 Introduction

ECOpure is a Nicotine containing preparation manufactured in the UK by Intellicig® NDD. ECOpure is manufactured for the use in NDDs as a vaporising liquid for direct inhalation into the mouth and lungs. It is available in both 20cc bottles and prepared cartridges. A range of flavours and strengths are also available including a Nicotine free preparation (Zero).

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3.0 Sponsor

CN Creative Ltd., Elap House, Fort Street, Accrington, BB5 1QG, UK.

4.0 Study Design

A randomised cross-over study to determine Nicotine bioavailability in moderate smokers using an Intellicig® NDD and a tobacco containing cigarette.

On day one of the study Subject Group 1 and Subject Group 2 will have blood samples collected at time Zero (T=0), immediately prior to smoking a cigarette, to determine blood plasma Nicotine levels prior to smoking. Blood samples will then be taken

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following the smoking of a cigarette at two minutes (T=2), five minutes (T=5), seven minutes (T=7), 10 minutes (T=10) and 30 minutes (T=30).

On day two of the study Subject Groups 1 and 2 will have blood samples collected at time zero (T=0), immediately prior to use of an Intellicig® NDD to determine blood plasma Nicotine levels prior to smoking. Blood samples will then be taken following the use of Intellicig® NDD at two minutes (T=2), five minutes (T=5), seven minutes (T=7), 10 minutes (T=10) and 30 minutes (T=30).

The use of both cigarette and Intellicig® NDD is standardised to one deep inhalation for five seconds and then four inhalations per minute for the time taken to smoke an entire cigarette. Each inhalation will last for four seconds and be held in the participant's lungs for four seconds prior to exhalation.

Number of participants: XX

5.0 Study Agents

ECOpure Medium(15mg/ml) Nicotine preparation for use in Intellicig® NDD.

Manufacturer: CN Creative Ltd, Elap House, Fort Street, Accrington, BB5 1QG.

Batch Release Site: CN Creative Ltd, UMIC, The Incubator Building, Grafton Street, Manchester, M13 9XX.

6.0 Evaluation Criteria

6.1 Safety Criteria

- Participants will be required to fill in a health questionnaire prior to participating in the trial. Participants will be verbally monitored through the duration of the trial for symptoms of Nicotine overdose, primarily headache and nausea.

6.2 Inclusion Criteria

- Informed Consent
- 18 years of age or older
- Current smoker

6.3 Exclusion Criteria

- History of heart disease
- Diabetes mellitus (NIDDM or IDDM)

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- Over the age of 65
- Currently using an NRT product
- Heavy smoker 20+ a day
- General ill health
- Pregnancy

6.4 Withdrawal Criteria

- Severe headache
- Nausea
- Other Symptoms of Nicotine overdose
- Light headedness
- Discretion of investigator
- Smoking 12 hours prior testing

7.0 Investigators

CN Creative Ltd. will be the investigators for this trial.

8.0 Adverse Events

Any adverse events during the study, whether related to the Nicotine preparation or device, will be assessed and recorded by the investigator. Adverse events may be either clinical or laboratory test abnormalities.

Serious adverse events must be reported to CN Creative Ltd. within 24 hours giving as much detail as possible. A complete report must be received within seven days of the adverse events becoming apparent.

Participants may leave the study either at their own wish or at the wish of the investigators. Reasons for participants leaving the trial must be recorded.

9.0 Necessary Approvals

Approval is not required from ethics board as no medicinal device or medicine is to be tested.

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10.0 Study Monitoring

All data remains the property of CN Creative Ltd. No publication in part or whole is permitted to be made without prior written consent from CN Creative Ltd.

11.0 Laboratory Analysis

Blood Samples will be drawn by Dr. XXXX XXXXXXXX

XXXXX Laboratories will carry out blood sample analysis.

XXXXX Laboratories, XXXXXX, XXX XXXXXXXX XXXXXXXX XXXXX XXXXXXXXXXXX
XXXXXXXXXXXXX

12.0 Results

Results from Blood Plasma Nicotine concentration show an average C_{max} for the Intellicig® NDD to be XXXng/mL. C_{max} for 0.5mg cigarettes were observed to be at XXXng/mL. C_{max} was reached at similar times for both the cigarette and Intellicig® NDD with an average time taken to reach C_{max} of 5 minutes 16 seconds.

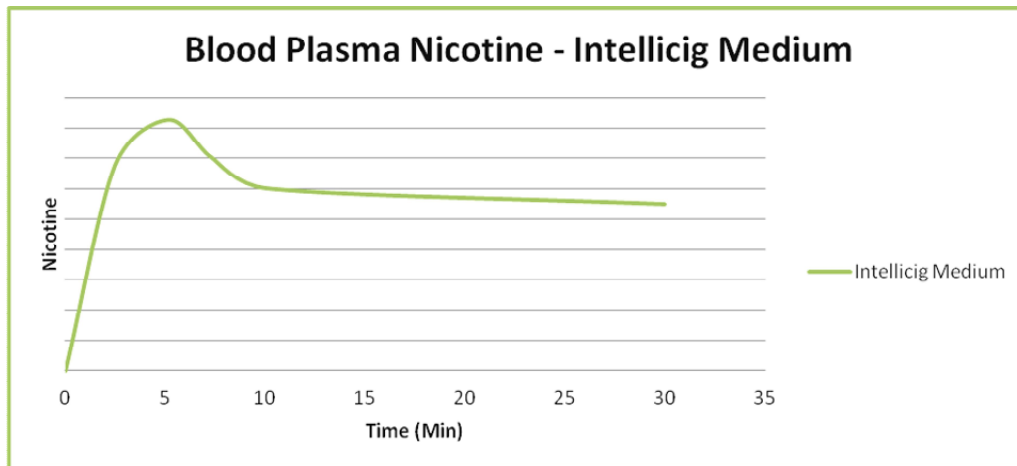


Figure 1 – Average Rate of Absorption of Nicotine from Intellicig in Venous Blood

From Figure 1 above it is evident that there is a steep initial rate of absorption between two and five minutes with the gradient of the line equating to xxx. The sharp rise in Nicotine concentration observed is understood to be responsible for alleviating Nicotine withdrawal symptoms and satisfying the craving at the nicotine receptor level.

When the subject groups smoked a cigarette containing 0.5mg Nicotine the kinetics of the average absorption were seen to be similar to that of the Intellicig® NDD.

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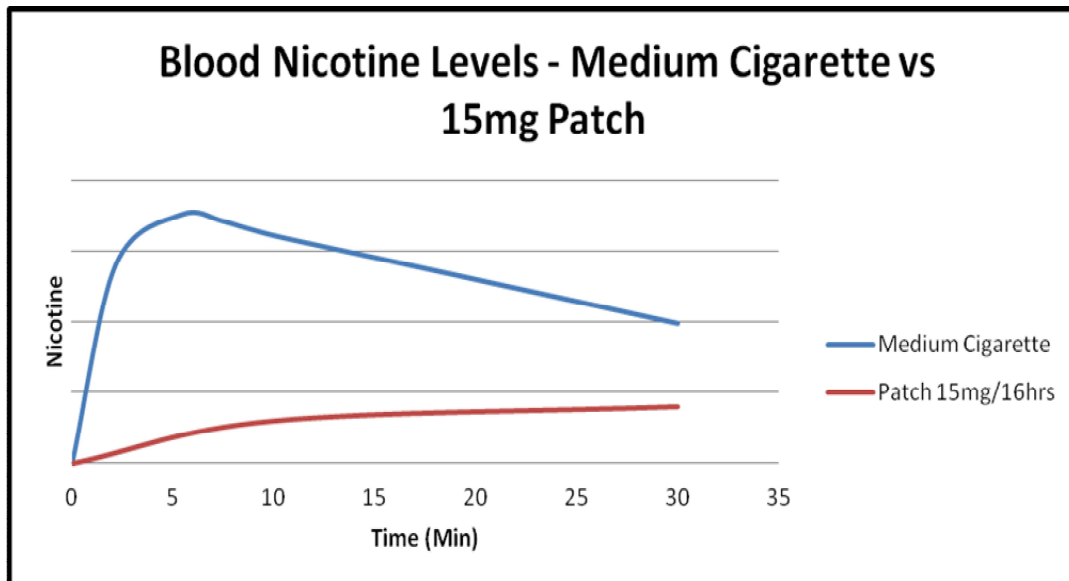


Figure 2 - Comparison of rate of absorbance of Medium Cigarette and 15mg Patch

From Figure 2 it can be observed that Nicotine absorption from cigarettes give a T_{max} (time at which C_{max} is reached) at 5 minutes 24 seconds (compared to 5 minutes 13 seconds for the Intellicig® NDD).

A comparison may also be made from published data on a Nicotine containing patch (15mg) designed to deliver Nicotine over a 16 hour period. Analysis of the rate of absorption of the patch shows a slow rate of absorption with a T_{max} at approximately 300 minutes (not shown in graph above).

	Cigarette 0.5mg	Intellicig® NDD	NiQuitin™ Lozenge 4mg*	Nicorette® Gum 4mg*
Time of C_{max}	5min 24sec	5min 13sec	45min	30min
Median (Full Range)	(5min to 10min 36sec)	(5min to 5min 26sec)	(10min 12sec to 120min 12 sec)	(19min 48sec to 60min)

Table 1 – Comparison of C_{max} of Cigarette, Intellicig®Med NDD, NiQuitin™ 4mg Lozenge and Nicorette® Gum 4mg

*Information derived from published data.

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13.0 Conclusion

From the above results it is possible to conclude that the Intellicig® NDD delivers a dose of Nicotine to the body with a similar T_{max} to that of a cigarette. It is the time taken to reach C_{max} , along with the Nicotine concentration in the blood, which is thought to be responsible for alleviating Nicotine cravings. Nicotine concentration must reach a threshold in the brain before receptor activation of the Dopamine reward system may occur, alleviating the symptoms associated with Nicotine withdrawal.

Comparison of the T_{max} of Intellicig® NDD and a 0.5mg cigarette show with only a 11 second time difference in time taken to reach C_{max} . It is this sharp rise in Nicotine level that is absent from many NRTs currently available and it is precisely this which is thought to alleviate Nicotine withdrawal symptoms.

Comparison of these results with published data on marketed NRT products suggests the Intellicig® NDD can deliver Nicotine at a much quicker rate than that of currently marketed NRT products. The downfall of many NRTs is thought to be a result of the lack of satisfaction from the Dopamine reward system. It is postulated that the Intellicig® NDD may deliver Nicotine in the correct timeframe as to satisfy the craving experienced by smokers, and so prove to be a successful NRT should MA be granted. It is thought that the cumulative effect of T_{max} and C_{max} at the correct times and concentrations is responsible for alleviating Nicotine withdrawal symptoms.

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