CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-714

PHARMACOLOGY REVIEW(S)

APR 8 1997

Review and Evaluation of Pharmacology/Toxicology Data
Division of Anesthetic, Critical Care & Addiction Drug Products
HFD-170 / Harry M. Geyer, III Ph.D.

NDA: 20-714

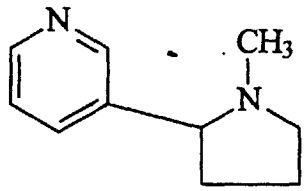
Completion Date: April 5, 1997

Sponsor: PHARMACIA & UPJOHN COMPANY

Drug Name: NICOTINE

Chemical Name: 1-methyl-2-(3-pyridyl)pyrrolidine

Structure:



NICOTINE

Relevant IND/NDA/DMF:

IND	
NDA #18-612	Nicorette gum
NDA #20-165	Nicoderm patch
NDA #20-385	Nicotine Nasal Spray

Drug Class: nicotine replacement

Indication: Smoking Cessation

Clinical Formulation : per cartridge; Nicotine (10 mg) and menthol (1 mg)

Route of Administration: inhalation (primarily buccal absorption)

Review Summary:
The general pharmacology / toxicology of nicotine is well documented in the literature and reviewed in previous nicotine INDs and NDAs.

Gastric absorption of nicotine
The sponsor has submitted one safety study with four dogs after oral administration of three nicotine containing plastic cartridges (30 mg total: 2.1 to 2.6 mg/kg), oral administration of nicotine solution (0.5 and 2mg/kg) and intravenous administration of nicotine (0.1 mg/kg), in a cross-over design. The cartridges contained less than 3% of the initial nicotine when retrieved from feces, but the peak blood levels were only 11-47ng/ml. The blood levels after oral solution administration were 3-12 ng/ml after the 0.5 mg/kg dose and the higher dose induced vomiting. The iv administration resulted in blood levels of 40-62 ng/ml with transient clinical signs, increased respiratory rate (4/4), salivation (4/4) and vomiting (3/4). After cartridge ingestion the

clinical sign was increased salivation (1/4).

The bioavailability of nicotine from the cartridges and the oral solution was less than 10% and the cotinine levels were 20-30 times nicotine, indicating a very significant first-pass metabolism. There does not appear to be a significant hazard upon oral ingestion of these cartridges.

Toxicity of nicotine by inhalation

The sponsor submitted several reports of inhalation toxicity with nicotine. One study (NI21208F) was done by the sponsor using rats with 5 days of nicotine inhalation at dose over 20 times the human exposure level. This study did not demonstrate any significant pathology induced by the nicotine exposure however, the limited number per group and the limited duration of exposure does not allow substantial conclusions of nicotine exposure by inhalation.

The remaining studies were from the literature, 26 weeks with 300+ hamsters, or from with rats breathing smoke from burning and non-burning tobacco. The studies generally support the lack of significant organ specific toxicity and the lack of or reversal of any airway histopathology. However, the lack of individual, and often group data, from these studies prevented any substantial review.

The nicotine vapor from the inhaler has no smoke particles to carry it deep in the lungs and a PET Scan study in humans with labeled nicotine (^{11}C) indicated that all the nicotine is deposited in the upper respiratory tract and absorbed by the buccal mucosa (#93NNIN007; V1.11-1.12). This study indicated that the present study may not be representative of the human condition although we do not know the actual deposition site for the nicotine droplets in the rats respiratory path. The pharmacology/toxicology is probably best characterized by previously reviewed studies of buccal absorption.

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Inhaler: Investigation of nicotine absorption in dogs after ingestion of inhaler cartridges

STUDY/REPORT NUMBER: 96031 [Nov. 6, 1996 subm.N(BM)]

STUDY SITE: Pharmacia & Upjohn
TSA, Helsingborg, Sweden

GLP/QA SPECIFICATIONS: "in compliance" Nov. 6, 1996 subm.N(BM)pg.3

SPECIES/NUMBER OF SUBJECTS/SEX: 4 female dogs (11.5 to 14.5 kg), four treatments in a cross-over design

DOSES/ROUTE OF ADMINISTRATION: PO cartridge, PO solution and iv solution

PROCEDURE:
The dogs were given three cartridges orally (10mg nicotine/cartridge), solutions of nicotine (0.5 and 2 mg/kg of nicotine) and iv bolus of nicotine (0.1 mg/kg); in a cross-over design. The blood levels of cotinine and nicotine were examined at 5, 15, 30 and 45 minutes; 1, 1.5, 2, 3, 4, 6, 8 and 24 hours after iv dosing and cartridge administration. The sampling after oral dosing initially followed the same schedule but was terminated after 2 hours. A week separated the different treatments.

RESULTS:
The cartridges were retrieved from the feces 12 to 24 hours after administration and contained less than 3% of the initial 10mg of nicotine. The peak nicotine blood levels were observed at 45 minutes in all four dogs and were between 11 and 47.1 ng/ml. The terminal $T_{½}$ was between 0.74 hrs to 1.17 hrs and the AUC were between 15 and 58 ng*hr/ml. The cotinine levels had T-max at one hour and the C-max was between 246 and 687 ng/ml.

After oral administration of a nicotine solution at 2 mg/kg dose, three of the four test dogs vomited and the sponsor did not consider the nicotine blood levels accurate. The presented data confirms this and maximum blood level was observed in dog #95058, 91 ng/ml at 30 minutes, and this dog had repeated vomiting between 23 and 31 minutes post-dosing. The dog with the lowest nicotine levels at 30+ minutes (<6 ng/ml) was #95052 which had the largest nicotine levels at 5 minutes (34.7 ng/ml) and repeatedly vomited 2 minutes post-administration.

The blood nicotine content after oral solutions at the dose of 0.5mg/kg nicotine peaked between 0.56 and 0.74 hours and the C-max was between 2.9 and 92.9 ng/ml. No clinical signs, such as vomiting were reported for this group. The cotinine levels had T-max at 0.5 to 0.75 hours and C-max was between 82.8 and 134.3 ng/ml.

The iv administration of nicotine at the dose of 0.1 mg/kg produced T-max values of 0.08 hours with C-max values of 46.8 to 92.9 ng/ml and clinical signs of increased respiration, heart-rate and salivation plus vomiting in 3/4 dogs. The cotinine levels had T-max between 0.25 and 0.5 hours and the C-max was from 16.7 to 23.3 ng/ml.

DISCUSSION:
Based on AUC values, the cotinine/nicotine ratios were between 1 and 2 for the iv administered nicotine and 20-30 for the oral capsules and the oral solution. The orally administered nicotine is showing a much greater first-pass metabolism and the bioavailability is less than 10% in the dog. As cited by the sponsor, the bioavailability of oral nicotine may be as high as 50% in humans and the risk estimate may therefore be underestimated by assessment in dogs. However, the present

study does not indicate a safety risk after oral ingestion of 3 cartridges in the dog and considering the size of the cartridge, the danger from ingestion may be more from the plastic cartridge than the nicotine content.

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Nicotine: Five day Inhalation

STUDY/REPORT NUMBER: 21208F NDA Vol.8/44 pg 70

STUDY SITE:

GLP/QA SPECIFICATIONS: According to

SPECIES/NUMBER OF SUBJECTS/SEX:
Rats, Sprague-Dawley with 5 rats per sex per treatment group. The rats were 6 to seven weeks old on arrival, 178 to 231g and acclimatized for 13 days prior to test initiation. The last seven days they were acclimatized to restraint in plastic tubes.

DOSES/ROUTE OF ADMINISTRATION:
Nicotine was administered through inhalation by head exposure to ambient air with control (0 µg/l), low (3.27 µg/l), medium (26.19 µg/l) and high (72.62 µg/l) concentrations of nicotine for two 90 minute session per day for 5 consecutive days. The rationale for dose selection was based on a Human Dose of nicotine. The sponsor calculated the Human Dose of nicotine by assuming 1.5 mg of nicotine/cigarette, 50 kg human, or 30µg/kg. Then, assuming an average exposure of 10 minutes and a respiratory minute volume of 15l/min, the mean nicotine concentration would be 10µg/l. The low dose was expected to be equivalent to 20 cigarettes/day in humans and the sponsor based a "safety factor" on the respiratory minute volume of 0.25l/min in a 250g rat.

PROCEDURE:
The rats were restrained in plastic tubes with their noses projecting into a chamber. The chamber was supplied with a flow of breathable air from compressed air cylinders and the nicotine mist was supplied to the incoming air by an ultrasonic generator placed below a solution of nicotine hydrogen tartarate dihydrate. The nicotine solution was supplied to the generator reservoir and flow rate was controlled by a needle valve. The particle size of the mist was analyzed and found to range from µm and therefore below the limit of respirable particles in the rat, up to 5µm.

The rats were exposed for two daily 90 minutes session for 5 days and a blood sample was taken

from the tail vein within 21 minutes of the second exposure on Days 1 and 5 and the samples were tested by the sponsor for nicotine and cotinine content.. After overnight fasting after the end of the 5 day test, the rats were sacrificed with pentobarbitone and full internal and external examinations were performed. This included assessment of any irritation to the respiratory tract. The nasal cavity was fixed intact and not examined.

RESULTS:
There were no deaths during the study and no treatment related clinical signs. The achieved dose levels, in mg/kg/day were 0.59 for the low dose group, 4.7 for the mid-dose group and 13.1 for the high dose group. The high dose group males consumed less food than control throughout the study and had significantly less body weight gain than control by Day 5.

There were no significant differences in the gross pathology at necropsy between the controls and any treatment group. The histopathology of the airway tissue in the control and high dose groups disclosed 1) inflammatory cell aggregates and lymphoid hyperplasia in the nasal cavity 2) inflammatory cell aggregates at the tracheal bifurcation 3) hyperplasia in the bronchi and 4) inflammatory cell foci and foamy histocytes in the lungs. However, the frequency in the air control group was not different than the frequency in the high dose group . There did not appear to be any significant increase in pathology at the high dose, but with a group size of 5/sex, the difference would need to be large for any statistical significance.

DISCUSSION:
One oral puff from the Nicotrol Inhaler releases about 7 µg of nicotine in 25 ml of air and one deep inhalation can release 50 µg in 200 ml of air as compared to a puff of a cigarette releasing 150-200 µg of nicotine. The nicotine vapor from the inhaler has no smoke particles to carry it deep in the lungs and a study in humans with labeled nicotine (^{11}C) indicated that all the nicotine is deposited in the upper respiratory tract and absorbed by the buccal mucosa (#93NNIN007; V1.11-1.12). This study indicates that the present study may not be representative of the human condition although we do not know the actual deposition site for the nicotine droplets in the rats respiratory path.

The sponsor assigned "safety factors" on dose levels of 20X, 157X and 436X, based on comparative respiratory minute-volumes in man and rats. However, if we use their calculation of the human dose of 30µg/kg/cigarette, then X20 cigarettes/day would come to 0.6mg/kg/day as a daily intake and this is equivalent to the low dose group (0.59mg/kg/day). The "safety factors" becomes 1, 8 and 22 for the three doses on a mg/kg/day basis and because there was no significant differences between controls and the high-dose group in terms of histopathology, the more conservative "safety factor" of 22X the average pack/day smoker can be accepted.

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THE SUBCHRONIC INHALATION TOXICITY OF NICOTINE IN THE GOLDEN HAMSTER (NI 5003: NDA V1.8 pg 210)

abstract and paper presented at IUPHAR 9th International Congress of Pharmacology, London 1984 - Poster Session 61 - Toxicology V // Clark, G. C., Lewis, D.J. and Rose, P.H. Huntingdon Research Centre, Huntingdon, Cambridgeshire, U.K.

This was a large 26 week study with 200 controls and 120 hamsters in each of four dose groups, 50%/50% according to sex. The nicotine was present in an aerosol in the chambers, 4.9, 16, 53 and 122 µg/l air concentrations for 5 x 30 minute exposures six days a week and 3 x 30 minutes on Sunday.

There were 19 animals that died or were sacrificed during the study but only two were possibly due to nicotine treatment. The blood levels on nicotine rose with chamber air concentration of nicotine and at 5 week the measured blood level in the high dose males was about 1.8µg/ml, nearly 100 x the therapeutic levels in the nicotine patches.

Except for excess salivation in the two higher dose groups, there were no clinical signs to differentiate treated animals from controls. In blood chemistry, the high dose group had minimal but significant increases in Alkaline phosphatase and blood urea. The cholesterol was slightly elevated in the high dose males and decreased in the females along with the triglycerides. The organ weights decreased with dose as did the body weights, the relative organ weight of the liver was increased in the high dose group at 14 and 27 weeks and fat deposition in periportal hepatocytes was increased in the high dose group from slight at 14 week to minimal or moderate at 27 weeks. A macroscopic pallor of the liver was observed frequently at sacrifice of the high dose group animals.

DISCUSSION:
These hamsters were exposed to nicotine in the air around the whole body and nicotine has significant dermal penetration. This makes the results difficult to characterize in relation to inhaled nicotine. However, the blood levels were very high and the lack of significant organ toxicity, other than some liver enlargement and lipid deposition, does add support to the general safety of nicotine.

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COMPARATIVE 90-DAY SUBCHRONIC INHALATION STUDY OF TEST MODEL 3 (TM-3) AND THE RJRT-2 REFERENCE CIGARETTE

(NDA:: V1.8 pg.220, 238, 270)

STUDY/REPORT NUMBER: NI 5002, 5059, 5060

STUDY SITE:

GLP/QA SPECIFICATIONS: unknown

SPECIES/NUMBER OF SUBJECTS/SEX: Rats; 30♂ and 30♀ in each of eight treatment groups

DOSES/ROUTE OF ADMINISTRATION: inhalation of nicotine in air; 5, 15 and 30 µg/l concentrations of both the *New Cigarette (TM-3)* non-burning and reference cigarette (RJRT-2), burning. Administration was one hour per day, five days a week, for 13+ weeks.

PROCEDURE: The section on toxicological end-points, hematological parameters, clinical chemistry, gross pathology etc. procedures was not included in this submission (6.2). The submitted procedures included blood COHb, plasma nicotine and cotinine, minute ventilation and special staining techniques for goblet cells.

This group of researchers used a smoke generator that actually smoked the reference cigarette and the TM-3 was designed to heat the tobacco to release the nicotine without burning. There was computer regulated production of a constant flow of mainstream smoke. The flow was adjusted to maintain the respective breathing air concentrations of 5, 15 and 30µg/l. A separate apparatus, without smoke generator, was used for controls.

RESULTS:

The plasma nicotine and cotinine concentrations were elevated in a dose related manner. The TM-3 groups of low, medium and high concentrations were 42.4, 126 and 238 ng/ml respectively. The corresponding cotinine levels were 12.1, 20.2 and 28.4 ng/ml (pg. 283).

The exposure results were close to the designed concentrations and the carbon monoxide (CO) exposures were 144, 394 and 698 ppm for the TM-3 group and 160, 459 and 864 ppm for RJRT-2 cigarettes. The blood COHb was definitely greater in the smoking groups and was approximately 12% in the low dose group and 42% in

the high concentration group (pg276).

The respiratory rates did not change significantly in the rats exposed to the non-burning smoke, however, the tidal volumes were generally less than controls and the minute-volumes were also slightly reduced (pgs278-282).

The non-burning tobacco groups definitely gained less body weight than controls for the 13 weeks of the study (-10%♂, -4.2%♀), but returned to control levels within an additional 4 weeks (pg 275).

There were no biologically significant alterations in serum chemistry, hematology or lipid chemistry, as stated by the sponsor of the study, Histopathology of the nasal passage were called similar in the controls and TM-3 groups with increased inflammation, hyperplasia and squamous metaplasia in the medium and high dose RJRT-2 group with burning tobacco smoke. Since none of this data was supplied the analysis is as stated by the sponsor and no review was possible.

DISCUSSION:

This addition of CO is definitely an additional toxicant not present in the Nicotrol Inhaler, making the comparison with Nicotrol Inhaler more difficult. In addition, the submitted data was without individual and group data thereby precluding any significant review. The most that can be obtained by this part of the submission is the concurrence with previous reviewed studies, that found non-burning nicotine administration to be relatively free of significant pathological consequences.

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Labeling Review: done and submitted to team leader, drug team and CSO.

RECOMMENDATIONS:

The reviewed studies do not indicate severe pathological alterations after inhalation of nicotine at concentration significantly higher than proposed human exposure. There are no unresolved pharmacology/toxicology issues and this product is approvable from the pharmacology perspective.

Harry M. Geyer III

Pharmacologist: Harry M. Geyer III, Ph.D.

Dou Huey (Lucy) Jean April 8, 1997

Team Leader: Dou Huey Jean, Ph.D.

cc: Orig NDA 20-714
HFD 170/Div File
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