

Description

Field of the Invention

The present invention relates to the cutaneous administration of nicotine, and more especially to a new method of administering nicotine through the skin using a transdermal delivery system, especially for the purpose of satisfying a nicotine habit while minimizing or eliminating side effects caused by absorbing tobacco constituents through the lungs along with products of combustion of tobacco.

Background of the Invention

The health hazards from tobacco smoking are well established. Of the approximately 4,000 by-products of combustion found in cigarette smoke, many of which are known carcinogens, the three substances studied most have been tars, carbon monoxide and nicotine. Tars and carbon monoxide have been directly implicated in the production or exacerbation of numerous health disorders.

Thus, tars are the causative agents in cigarette smoke most implicated in the induction of such cancers as lung, larynx, oral cavity, esophageal, bladder, kidney, pancreatic stomach, and uterine and cervix cancers. Tars are also considered responsible for the induction of the hepatic microsomal enzyme systems which result in more rapid deactivation of a variety of drugs such as benzodiazepines as well as anti-depressants and analgesics. Tars are also responsible for the production of broncho pulmonary diseases, including pulmonary emphysema, chronic bronchitis and smokers respiratory syndrome.

Carbon monoxide, a deadly gas, is an important health hazard even in minute quantities because it combines with the hemoglobin in the blood so that the hemoglobin can no longer carry sufficient oxygen. Moreover, the stimulant effect of the nicotine in the smoke causes an increase in cardiac workload and oxygen demand, whereas the carbon monoxide effectly blocks the ability of the heart muscle to capture the needed oxygen. In other words, carbon monoxide and nicotine work together in a synergistically negative manner in a way which often results in anoxia and ultimately in cardiac damage. In addition, carbon monoxide has also been implicated as a causative agent in the development of such disorders as coronary artery disease and atherosclerosis.

Nicotine appears to be the most pharmacologically active substance in tobacco smoke, yet it appears to be not as significant from a health standpoint as the tars and carbon monoxide. However, nicotine is very important from another stand-

point, i.e. it is the reinforcing substance in tobacco which maintains the addiction. In this respect, a theme commonly heard among workers in the field of smoking research is, "People would be disinclined to smoke cigarettes if an alternate route of nicotine delivery could be devised.

Several such attempts have been made to administer nicotine in alternate ways, but with varying and generally ineffective results. For example, nicotine-containing pills have been studied; however, effective blood levels of nicotine are not achieved because drugs absorbed in the stomach pass through the liver first where, in this case, 80-90 percent of nicotine deactivation occurs. Similar findings have been demonstrated with nicotine chewing gum although it has been sufficiently successful to warrant its marketing.

There are other long established and traditional ways of absorbing nicotine through the mouth, including chewing tobacco, snuff and the newly introduced products such as "Bandits" which constitute diffusion bags of tobacco, all of such means relying on oral (or nasal) absorption of nicotine through the mucous membrane. However, because of the taste and other sensory effects of tobacco, such a manner of satisfying the nicotine habit is acceptable to only a very limited number of persons. Moreover, these habits still require the utilization of tobacco, and such use remains a problem especially for people with gum, mouth or throat problems as a result of long-term tobacco chewing or snuff "dipping" and who are unable to quit.

With regard to the nicotine gum referred to above, it has produced mouth ulcers in a number of individuals resulting in its rejection. In addition, the nicotine gum produces some gastric absorption with the resultant first pass through the liver and consequent rapid loss of activity. Moreover, first hand reports indicate that some people using the gum rejected it on the basis of taste. Moreover, denture wearers have difficulty with gum in general; this is important as many people who experience the medical problems associated with years of smoking may also be denture wearers.

Nicotine itself has been subjected to considerable study. Nicotine is a liquid alkaloid which is colorless, volatile and strongly alkaline. On exposure to air it turns brown. It is known to be very lipid soluble. The Merck Index, 9th Edition, 1976, page 847, indicates that nicotine base is readily absorbed through mucous membrane and intact skin, but the salts are not. On the other hand, nicotine has no known therapeutic application (The Pharmacological Basis of Therapeutics, fifth edition, Goodman and Gilman, 1970, page 467) and has been primarily used in research as an experimental tool for investigating neural function.

It is known to administer a wide variety of pharmaceuticals transdermally through the skin, and two patents which disclose bandages for administering drugs are the Zaffaroni U.S. patents 3,598,122 and 3,948,254. Drugs indicated to be administerable include anti-microbials sedatives, hypnotics, psychic energizers, tranquilizers, hormones, anti-pyretics, anti-diabetics, cardiovascular agents, anti-spasmodics, anti-malarials, decongestants, nutritional agents, anti-bacterials, anti-neoplastics, anti-inflammatory agents, desensitizing agents, vaccines, anti-allergics, anti-fungals, anti-perspirants, deodorants, astringents and irritants. Thus, while the field of drugs and pharmaceuticals mentioned in these patents is very wide, there is no disclosure of administration of nicotine; and nicotine appears to have few properties in common with the categories of drugs mentioned in these patents. In view of the fact that nicotine has no therapeutic use, its relationship to any agents mentioned in these patents appears even more remote.

It is further known that the absorption of many topically applied drugs may be enhanced by occlusion, which consists of covering the treated skin with an impermeable plastic sheet or film which prevents water evaporation or drug decomposition. Under such circumstances the keratin layer then becomes softer and less effective as a bearer, so that absorption of the drug is facilitated (Annual Review of Medicine, Volume 33, Chapter 18, 1982, "The Principles of Drug Therapy in Skin Disorders", R.C. Heading, pages 475-476).

DE-A-3 438 284 discloses a pad containing nicotine for transdermal administration. It assumes that depot plasters with a structure adapted for medicaments may also be used for administration of nicotine.

US-A-3598122 discloses two different plasters. In one case, a liquid drug is released from a container through a rate controlling membrane. In a separate case, the drug is contained in an absorbant matrix.

The object of the invention is to provide a specific structure for a device for transdermally administering nicotine at a controlled rate taking into account the highly toxic nature of this substance.

SUMMARY OF THE INVENTION

This object is achieved by the features of claim

1. Using such a device provides a number of beneficial results as follows:

1. An improved system becomes available to aid motivated smokers in eliminating their cigarette addiction. Numerous potent non-pharmacological factors which help maintain the cigarette addiction are the rituals involved with the act of

smoking, including the sight of a pack of cigarettes, the smell, the taste, etc. These previously neutral cues acquire powerful reinforcing properties as a result of prolonged associations with nicotine. Practice of the present system, however, assists in extinguishing these addiction-maintaining cues by supplying nicotine in the absence of such cues.

Indeed, a plurality of extinguishing techniques can be utilized in association with the present invention. Thus, instead of completely substituting the technique of the instant invention for smoking, an interspersing regimen can be adopted wherein nicotine-containing transderms according to the invention may be alternated with cigarettes to slowly extinguish the reinforcing properties of the non-pharmacological factors, and also reduce the severity of the initial termination of smoking as well as the incidence of relapse. As the non-pharmacological factors become reduced in importance, it then upon becomes easier to treat the nicotine addiction.

2. Patients with disorders such as emphysema, cardiac problems or lung cancer and who are unable to quit smoking thus exacerbating their medical problems are able to satisfy their nicotine habit while sparing themselves further damage from the tars and carbon monoxide in tobacco smoke.

3. Nicotine absorbed transdermally is not transported first pass through the liver where 80-90 percent of nicotine deactivation occurs, but goes directly and rapidly into systemic circulation with rapid rises in nicotine blood level. Thus, the nicotine habit can be satisfied while subjecting the body to far lesser quantities of nicotine.

4. Using the present device, blood levels of nicotine can be easily adjusted to acceptable and effective dosages for the suppression of craving by varying the amount and duration of nicotine delivery. This is difficult if not impossible to accomplish with nicotine gum, because the person's rate of chewing is a major factor which manipulates dosage.

5. People with gum, mouth and throat problems, as a result of long-term tobacco chewing or snuff "dipping" and who are unable to quit, are aided in giving up their habits with the use of transdermally applied nicotine.

Other advantages compared to nicotine containing gum include obviating the problems of mouth ulcers in some individuals; elimination of nicotine taste as a secondary reinforcer; provision of a less conspicuous form of nicotine consumption (a cutaneous patch is much less conspicuous than gum chewing; for example, in stressful situations which typically serve as cues for smoking, such as business meetings, etc.,

gum chewing is less acceptable than the use of a transdermal patch); usability by those who reject the gum on the basis of taste and some denture wearers who cannot chew gum; and provision of an alternate mode of nicotine administration. In this latter respect, even if the transdermal administration is only equal in effectiveness to nicotine gum for many persons, this will provide a further method of reducing smoking dependence, it being known in the field that different techniques work better for different individuals.

7. In the event that the subject of the instant invention becomes available over-the-counter (as are cigarettes, snuff, chewing tobacco, etc.), the instant invention will provide a means for those, unable or unwilling to quit smoking, to ingest nicotine without subjecting themselves and their environment to smoking with its attendant dangers of carbon monoxide and tars. It would also allow ingestion of nicotine in places where smoking is prohibited, to avoid the consequences of performance decrements resulting from acute withdrawals. Moreover, for women unable to quit smoking during pregnancy, transdermal nicotine would at least eliminate carbon monoxide, thereby avoiding the deleterious effects of smoking on the fetus due to the blocking effects of carbon monoxide on oxygen absorption.

Brief Description of Drawing

For a better understanding of the invention, as well as the above and other objects and the nature and advantages of the instant invention, possible embodiments thereof will now be described with reference to the attached drawing.

The drawing is a schematic cross-sectional view of an embodiment according to the present invention.

Detailed Description of Embodiments

The drawing shows an embodiment of a nicotine bandage 110 having a nicotine impermeable backing 112 with a relatively large cavity 114, covered with a nicotine permeable membrane or microporous film 118. The reservoir 114 is surrounded with adhesive 120. Located within the cavity is a suitable absorbant material 122, such as cotton, on which is absorbed the desired quantity of liquid nicotine, preferably in the range of 1-4 microliters to provide a dosage desirable in the range of about 15-25 nanograms per liter of blood per administration.

Dosage and duration of nicotine administration transdermally according to the present invention

can be controlled in several ways separately and in combination. In general, a carrier can be mixed with the nicotine which will either speed or slow its passage through the microporous membrane and/or into the skin. The thickness, number of pores and/or size of pores can be varied to either increase or decrease the speed of passage of nicotine through the microporous membrane. The quantity of nicotine in the reservoir can be either decreased or increased to reduce or increase the duration or amount of dosing.

In general, no additive is necessary to assist in the transdermal administration of nicotine, because nicotine base is very highly lipid soluble and is quickly and completely absorbed into the systemic circulation. However, should it be desirable to increase or decrease the rate of penetration, then the nicotine base can be carried by a suitable solvent such as propylene glycol, glycerin, mineral oil, polyethylene glycol, DMSO or alcohol. It may also be mixed with water in which the alkaloid is readily soluble, thereby forming a water soluble salt; such a salt, however, is less lipid soluble and penetrates the skin much more slowly than the alkaloid base.

It may be desirable to add a carrier which will slow absorption in view of the fact that nicotine is highly toxic. In this way, the nicotine may be diluted to reduce dangers of misuse; for example, the nicotine may be mixed with an oil such as indicated above, or preferably an oil having an unpleasant taste, such as castor oil. Other types of fillers may be utilized as well; for example, the nicotine may be retained in a gelatinous base. Other additives may be incorporated to reduce the possibility of accidental oral ingestion, such as a mercaptan.

Using transdermal delivery while varying the porosity of the membrane separating the nicotine from the person's skin and/or the quantity of nicotine and manner in which it is retained, the dose and duration of nicotine administration are precisely controllable. Also, the total dosage and delivery rate can easily be adjusted to suit the needs of the particular patient, i.e. a different dose of nicotine will be desirable to reduce the craving of a one pack-a-day smoker versus a three pack-a-day smoker. According to the present invention, it is possible to mimic smoking in terms of the amount of nicotine delivered, thereby reducing or eliminating dependency on any form of tobacco.

The nicotine is administered transdermally using an occlusive technique, i.e. the use of a pad in which the backings (e.g. backing 112 in the illustrated embodiment) are impermeable and opaque to provide protection from light and air so as to insure transport across the skin before the nicotine has a chance to become deactivated.

It is preferred that the pad 110 or the like be placed inconspicuously on the area of the skin such as behind the ear. This postauricular area insures rapid transport to the brain with little blood dilution. Alternatively, the pad can be placed elsewhere such as on the underside of the wrist, in which case there is delayed transport of the nicotine to the brain with enhanced blood dilution. The particular areas selected is determined on the basis of the severity of the addiction. The onset of nicotine activity is in the range of 1-2 minutes with a duration of action up from 30-45 minutes, these values varying as a function of the dose administered, the permeability of the porous membrane, the surface area covered by the nicotine, and the site of application.

The following example further illustrates the present invention.

Example

A bandage is made as shown in Fig. 2 comprising an occlusive pad 110 with a backing 112 approximately 1.5 cm in diameter and having an open reservoir 114 covered by a nicotine impermeable sealant film to be removed before application of the pad 110 to the skin. The open reservoir 114 contains a dense matrix of inert fibrous material, such as cotton, to prevent spillage of the nicotine prior to application of the pad to the skin. In use, the nicotine wicks from the cotton matrix as the nicotine diffuses across the skin.

Claims

1. A device for administering nicotine for assisting a person to quit smoking or for the purpose of satisfying a nicotine habit while minimizing or eliminating side effects caused by absorbing nicotine through the lungs along with products of combustion of tobacco, comprising a pad (110) to be adhered to the skin and transdermally administering nicotine at a dosage rate sufficient to satisfy said nicotine habit, characterized in that said pad (110) is occlusive and comprises a nicotine-impermeable backing (112) defining a cavity (114) therein, and an inert fibrous material (122) having absorbed nicotine therein, within said cavity (114), said cavity being covered by a nicotine-permeable, porous, inert membrane (118).
2. A device according to claim 1, wherein said nicotine is in the form of nicotine base without a solvent, vehicle or carrier.

Patentansprüche

1. Einrichtung zum Verabreichen von Nicotin, um einer Person zu helfen, das Rauchen abzugewöhnen und zum Zwecke der Befriedigung der Nicotinsucht, wobei gleichzeitig Nebeneffekte minimiert oder eliminiert werden, die durch die Nicotinaufnahme durch die Lungen im Zusammenhang mit tabakverbrennenden Produkten hervorgerufen werden, mit einem auf die Haut zu klebenden Pflaster (110), das durch die Haut Nicotin mit einer Zufuhr rate verabreicht, welche ausreicht, um die Nicotinsucht zu befriedigen, dadurch gekennzeichnet, daß das Pflaster (110) abgeschlossen ist und eine für Nicotin undurchlässige Unterlagsschicht (112), die einen Raum (114) definiert, sowie im Raum ein inertes faseriges Material (122) aufweist, das Nicotin absorbiert hat, wobei der Raum durch eine Nicotindurchlässige, porige und inerte Membran (118) bedeckt ist.
2. Einrichtung nach Anspruch 1, dadurch gekennzeichnet, daß das Nicotin in der Form einer Nicotinbase ohne Lösungsmittel, Vehikel oder Träger vorliegt.

Revendications

1. Dispositif pour l'administration de nicotine à une personne en vue de l'aider à cesser de fumer ou pour satisfaire un besoin en nicotine tout en minimisant ou éliminant les effets secondaires provoqués par l'absorption de nicotine au travers des poumons en même temps que les produits de combustion du tabac, comprenant un timbre (110) destiné à être collé à la peau et à administrer par voie transdermique la nicotine à un dosage suffisant pour satisfaire ledit besoin en nicotine, caractérisé en ce que ledit timbre (110) est occlusif et en ce qu'il comporte un support (112) imperméable à la nicotine définissant une cavité (114), et un matériau fibreux inerte (122) renfermant de la nicotine absorbée, à l'intérieur de ladite cavité (114), ladite cavité étant recouverte d'une membrane (118) inerte poreuse et perméable à la nicotine.
2. Dispositif selon la revendication 1, dans lequel ladite nicotine est sous la forme de nicotine base sans solvant, véhicule ou support.

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