Use Of Transdermal Nicotine Systems In A Possible Suicide Attempt

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Background: **Transdermal drug delivery systems, a relatively recent development, are well accepted by physicians and patients because of reliability and ease of administration. The patch reservoirs, however, contain large quantities of drug, and the potential for considerable toxicity exists if they are used incorrectly. A case is presented of an apparent suicide attempt that involved the use of nicotine transdermal patches.**

Methods: **This case report involved a patient seen in the emergency department by one of the authors. Data were obtained from the patient's medical record while maintaining confidentiality.**

Results: **The drug overdose was a potentially serious one. The patient recovered fully after an uneventful hospital course.**

Conclusions: **Transdermal drug delivery systems now deliver many drugs, several of which are quite potent. Intentional or unintentional misuse of the systems can result in toxicity. The physician and pharmacist should carefully instruct each patient in the appropriate use and handling of transdermal drug delivery systems. (J Am Board Fam Pract 1994; 7:417-20.)**

With the advancement of transdermal technology, such pharmaceutical agents as estrogen, scopolamine, nitroglycerin, fentanyl, and recently nicotine can be administered by the transdermal route. Transdermal administration is not typically associated with acute drug overdosage, but the following case appears to illustrate an attempt at suicide using transdermal nicotine patches in combination with ingestion of other substances. Following the case presentation, we discuss the symptoms and the treatment of nicotine toxicity and recommend safety guidelines to consider when prescribing transdermal nicotine therapy.

Methods

The case report was developed from information described by the attending physician and from the patient's medical record. The patient's confidentiality was maintained. References for background literature were obtained from bibliography review, MEDLINE, and *International Pharmaceutical Abstracts*. Key words used to search included "nicotine," "toxicity," "poisoning," "toxicology," "treatment," "management," and "contaminant."

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Background

Nicotine is one of the most toxic of all poisons and acts with great rapidity. It is well absorbed from the gastrointestinal and respiratory tracts and through intact skin. Percutaneous absorption occurs many times more rapidly with the free alkaloid than with any of its acid salts.[1,2]

The major effects of nicotine, in addition to local caustic action, are transient stimulation and then subsequent depression or paralysis of the central nervous system, all peripheral autonomic ganglia, and motor end-plates in skeletal muscles. Nicotine exerts an excitatory effect on smooth muscle, which could be responsible for the vasoconstriction and gastrointestinal hypermotility that are observed following toxic exposures.[1] Fatalities are traditionally believed to result from respiratory arrest secondary to muscle paralysis, although there is now evidence that central depressant effects might contribute as well.[2,3]

A lethal dose of nicotine in adult humans is estimated to be 30 to 60 mg or 0.5 to 1.0 mg/kg. Tolerance to the toxic effects of the alkaloid can be acquired by habitual smokers, however, and persons ingesting as much as 2.0 g of nicotine have survived.[4] In fatal poisonings death is rapid, usually occurring within 1 hour and occasionally within 5 minutes.[1] Artificial ventilation and

circulatory support are often effective in preventing death, and some patients have experienced complete recovery within hours.[1-4]

Most fatalities associated with nicotine poisoning occurred in the 1920s and 1930s, when concentrated nicotine solutions were commonly used as insecticides, and reports of fatal poisonings frequently involved the mistaking of nicotine solutions for other medications.[2] Between 1930 and 1935, 288 nicotine-associated fatalities occurred in the United States.[5] Nonfatal poisonings were much more common than fatalities, however, with some serious illnesses resulting from percutaneous exposure through clothing to as little as 7.5 mL of concentrated nicotine solution.[5-9]

Symptoms of nicotine toxicity are manifested primarily by the gastrointestinal tract and the central nervous system. Features of gastrointestinal cholinergic overstimulation are prominent and include severe nausea, vomiting, salivation, and diarrhea. Central nervous system signs and symptoms include headache, dizziness, confusion, seizures, and coma. In addition to central nervous system and gastrointestinal manifestations, severe nicotine toxicity results in increased heart rate and blood pressure and respiratory muscle paralysis, which are the events that can cause death.

Treatment of nicotine poisoning includes removing external sources of exposure, decontaminating the gastrointestinal tract if vomiting and diarrhea have not occurred, administering oxygen, and supporting respiration and circulation, if necessary. In cases of nicotine toxicity caused by transdermal patches, removing the patches and washing the application sites with water only are recommended. The use of soap can actually drive nicotine on the skin surface further into the skin, thus increasing the amount absorbed.[10-13] Signs of toxicity are self-limiting, and recovery usually occurs rapidly following discontinuation of exposure.

Nicotine is eliminated primarily by the liver, and approximately 20 metabolites have been identified. Following intravenous infusion, the plasma half-life of nicotine is 1 to 2 hours in individuals with normal hepatic function. The lung and kidney also metabolize small amounts of the drug. During percutaneous absorption of nicotine, no important metabolism occurs in the skin. Nicotine has a large volume of distribution of 2 to 3 L/kg.[14] Plasma half-life with a nicotine patch in place is 11 to 12 hours, which reflects continued percutaneous absorption of drug, and following removal of a nicotine patch, absorption continues for several more hours, indicating the persistence of a cutaneous reservoir of drug.[15] Plasma nicotine levels in nonsmoking volunteers are undetectable in 10 to 12 hours following patch removal but would be expected to decrease more rapidly in smokers whose hepatic enzymes have been induced by the polycyclic aromatic hydrocarbon components of smoke.

Four nicotine transdermal patches are currently approved for use and marketed in the United States: Nicotrol (Parke-Davis), Nicoderm (Marion Merrell Dow), Habitrol (Basel-Ciba-Geigy), and Prostep (Lederle). All of the patches are applied every 24 hours, for 24 hours, except for Nicotrol, which is applied every 24 hours but removed at bedtime, for an effective application time of approximately 16 hours. All patch strengths contain varying amounts of nicotine (Table 1), but all brands contain nicotine as the free alkaloid, which is the form most readily absorbed through the skin.[10-13]

Percutaneous absorption from the drug-impregnated patch reservoir is generally excellent, but to maintain a drug gradient across the system membranes, a substantial amount of drug must remain in the controlled-release system after the 16-hour or 24-hour administration period (Table 1). For this reason safe disposal of the used patch is of the utmost importance, because children or pets discovering the used patch could be poisoned by the remaining nicotine.

Case Report

A 15-year-old girl had a reported history of adjustment disorder with depressive features and attention deficit disorder. She had a history of three previous suicide attempts. On the evening of admission to the emergency department she was found unresponsive, lying on her bed. She was last seen at 4 PM in her usual state of health. Her parents discovered her at 6:45 PM and telephoned for emergency services. On arrival, the paramedics found the patient responsive only to deep pain. She had placed 14 Habitrol patches on her chest, abdomen, buttocks, and extremities. It is unknown how long the patches were in place. Paramedical personnel removed 12 of the patches, and the 2 remaining were removed in the emergency

Table 1. Characteristics of Nicotine Transdermal Systems.

Product	Nicotine Dose Absorbed (mg/24 hr)[10-13]	Time to Peak Plasma Concentration (hours)[10-13]	Total Nicotine Content (mg)[10-13]	Residual Nicotine (mg) after 24 hours[10-13]	Maximum Plasma Concentration (ng/mL)
Nicoderm	21	2–4	114	83	23
(Marion Merrell Dow)	14		78	60	17
	7		36	26	8
Habitrol	21	5–6	52.5	31.5	17
(Basel)	14		35	21	12
	7		17	10.5	7
ProStep	22	8	30	8	16
(Lederle)	11		15	4	ND
Nicotrol	15*	8	24.9	6	13
(Parke-Davis)	10*		16.6	4	7
	5*		8.3	2	3.5

ND=No Data
*Nicotine absorbed over 16 hours

department. The size and milligram strength of the patches were not known. On examination at the emergency facility her respirations were regular at 12/min, blood pressure was 170/92 mm/Hg, and pulse was 60 beats/min. Her skin was cool and clammy. She continued to be responsive only to deep pain, which elicited withdrawal. Her pupils were dilated with normal light reflex. Gastrointestinal signs were not present and were not reported by paramedics during transport. The remainder of her examination was unremarkable.

The patient was washed with soap and water and received activated charcoal by orogastric tube. Approximately 45 minutes after arrival at the emergency department, she regained consciousness and slowly returned to her base-line mental status. On further questioning, the patient admitted she had also ingested "small" quantities of her mother's other medications obtained from a medicine cabinet, which included ranitidine, alprazolam, co-trimoxazole, and ibuprofen. Blood concentrations for these medications were not obtained. A laboratory toxicology determination was positive for amphetamine and negative for ethanol, acetaminophen, and benzodiazepines. Initial laboratory data included white cell count 9500/μL, hemoglobin 14.1 g/dL, and hematocrit 43.7 percent; liver function tests were within normal limits. Arterial blood gases on 6 L of oxygen were pH 7.40, pCO_2 37.0 mmHg, pO_2 97 mmHg, bicarbonate 23 mEq/L, oxygen saturation 98 percent. An electrocardiogram revealed sinus bradycardia. She was admitted to the intensive care unit, where her hospital course included cardiac, respiratory, and mental status monitoring and supportive care. Her recovery was rapid and without complication; she was discharged after 48 hours to the psychiatric unit for further care.

Discussion

Although neither a urinary cotinine level (the primary metabolite of nicotine) nor a blood nicotine level were obtained, this case serves to draw attention to a potentially serious or fatal situation. We are reluctant to claim that this patient's physical examination and presentation are consistent with nicotine toxicity. Evidence to support nicotine toxicity would have included vomiting, diarrhea, salivation, tachycardia, coma, and a rapid return to base-line mental status after removal of patches. The patient did appear comatose, experienced a rapid recovery, and had an elevated blood pressure that decreased over several hours, and these findings do suggest nicotine toxicity. Interestingly, multiple substances were claimed to have been ingested, but they were not detected, and other substances were detected but not suspected. Nevertheless, the use of nicotine patches as a source of drug overdose was undeniable and potentially very toxic.

It is important for the clinician to recall that there are differences among the patches in nicotine absorption rates and bioavailability (Table 1). Contact time with the skin is important, and although plasma nicotine levels were not measured, if our patient had had the patches on for more than a few hours, the absorption could have been extensive. Absorption of nicotine from a transder-

mal patch is also influenced by application site, and data indicate that absorption rate is slightly more rapid from sites over the chest.[11] The importance of patch placement with regard to toxicity is unknown.

In light of the potential for unpleasant or serious toxicity resulting from intentional or unintentional misuse of nicotine patches, we recommend that the following guidelines be given to all patients receiving transdermal nicotine therapy:

1. Do not use tobacco products while being treated with nicotine replacement patches. Blood nicotine levels remain elevated for 6 to 12 hours after removal of a patch.[12-15] Toxic side effects or serious adverse reactions, such as nausea, increase in blood pressure, dizziness, abdominal pain, sweating, or chest pain, can occur. If you experience any of these reactions, contact your physician.
2. Be certain that your physician and pharmacist are aware of *all* medications you are taking. Many commonly used medications can change the rate at which the body is able to excrete nicotine that is absorbed from the patch. The consequences could be either increased side effects from the nicotine or a failure of the patch to control your urge to smoke.
3. Patches are medication, as are tablets or capsules; store them well out of reach of children and pets.
4. Dispose of used patches carefully by first folding them with the sticky sides together and then wrapping them in the package from which the new patch was removed. Dispose of used patches safely, away from children and pets. Call a poison control center, physician, pharmacist, or hospital emergency department if you have questions.
5. Trim, but do not shave hair at the intended application site. Irritation caused by shaving can increase nicotine absorption.
6. To remove nicotine after application, wash hands with water only. After applying or removing a patch, do not touch your eyes or nose before washing your hands.
7. The most common side effect of the nicotine patch is irritation of the skin under and surrounding the patch. If this irritation is severe, remove the patch and contact your physician.
8. Nicotine in any form is not safe to use during pregnancy. If you are pregnant or suspect you may be pregnant, discontinue use of nicotine immediately and contact your physician.

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