

Effects of Heat on Transdermal Drug Patches

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Background

Transdermal drug delivery has been around since 1979, with *Transderm Scop* being the first FDA-approved transdermal drug delivery system. Today, a number of drugs are available in transdermal dosage forms (e.g., estrogens, testosterone, clonidine, nitroglycerin, scopolamine, fentanyl, lidocaine, and nicotine). One of the major advantages of transdermal drug delivery is the steady delivery of drug, resulting in consistent drug levels. Another advantage is the convenience of weekly or bi-weekly application resulting in improved patient compliance.

The major barrier to transdermal drug delivery is the skin. Drug compounds are thought to transfer through the skin by passive diffusion.¹⁻³ Once diffusion through the multiple layers of skin is achieved, the drug molecules are absorbed by the capillary plexus and are then transferred into the general circulation by local blood vessels.¹⁻³ The absorption of the drug into the systemic circulation is regulated by skin permeability and local blood flow.³

Effects of Heat

Heat is known to increase skin permeation of drugs by several mechanisms. Higher temperatures increase microcirculation and blood vessel permeability, which facilitates drug transfer into the systemic circulation.^{3,4} A rise in temperature may also increase drug solubility both in the patch formulation and within the skin, thus increasing the release rate of the drug from local skin tissue into the systemic circulation.^{3,4} In fact, a new technology utilizing heat's ability to increase transdermal permeation called the controlled, heat-aided drug delivery (CHADD) system is currently under review by the FDA.^{4,5}

Since heat increases skin permeation, there are concerns that excessive exposure to heat will increase absorption of transdermally delivered drugs and lead to overdosage. In fact, the U.S. prescribing information for *Duragesic* warns patients to avoid exposing the application site to direct external heat sources, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, and heated water beds, etc., while wearing the patch.⁶ In addition, the Canadian *Duragesic* drug monograph also warns patients to avoid hot water bottles, hot whirlpool spa baths, and intensive sun-bathing.⁷ A pharmacokinetic model showed that serum fentanyl concentrations could theoretically increase by approximately one-third for patients with a body temperature of 40°C (104°F).⁶ Therefore, the manufacturer also recommends close monitoring for opioid side effects in patients who have developed fevers while wearing a *Duragesic* patch.^{6,7}

Case Reports

Several case reports of fentanyl overdose due to exposure of fentanyl patches to heat have been published.^{8,9,10} One patient inadvertently placed a heating pad over her fentanyl patch and was found to have symptoms of opioid overdose after two hours.⁹ Another patient was given a heating blanket that covered her fentanyl patch during surgery. Throughout the surgery, her respiration decreased steadily and upon examination, her pupils were pin pointed bilaterally.¹⁰ In a third case, a normally sedentary man wearing fentanyl patch participated in various outdoor activities, including swimming, hiking, and playing ball and was later found unresponsive. The author concluded that the increase in outdoor activities, combined with the sunny and warm weather caused a rise in the patient's body temperature and thus increased fentanyl absorption.¹¹

There is also a recent report of increased estrogen absorption after several days of sun tanning while wearing a *Climara* patch. The woman experienced hot flashes before the end of her dosing cycle, and noticed dark spots where her patch had been applied. It's suspected the exposure to excessive heat caused an early release of estrogen from the patch.¹²

Studies

Results of several small studies have shown that an increase in skin blood flow during heat exposure can dramatically alter the pharmacokinetics of transdermally administered drugs.³ Barkve et al conducted a study where 12 healthy volunteers wore nitroglycerin patches during a twenty minute sauna. The mean

plasma concentration of nitroglycerin was three times higher during the sauna exposure as compared to a control session at room temperature. A significant fall in diastolic blood pressure and an increase in heart rate were also observed.¹¹

Another study examined the influences of bathing and hot weather on the pharmacokinetics of transdermal clonidine system, M-5041T. The study found a significant increase (150% to 200%) in the plasma concentration of clonidine during the summer trial as compared to the winter trial.¹²

Interestingly, the pharmacokinetics of the contraceptive patch *Ortho Evra* were not altered under conditions of heat, humidity, and exercise in a study conducted by Abroms et al.¹³

Summary

Heat-induced increased absorption of transdermally delivered drugs is well documented.⁶⁻¹² However, many patients are not aware of the possibility of overdosing on transdermally delivered drugs when the application site is exposed to heat. It is important to educate patients about this possibility to prevent drug overdose and/or compromise efficacy. Patients should be advised to avoid exposing the patch application site to external heat sources including, but not limited to, heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, hot water bottles, hot whirlpool spa baths, and intensive sun-bathing. They should also be advised that fever and an increase in body temperature from intense physical activity may also increase the absorption of transdermally delivered drugs. In the event of drug overdose, the drug patch should be removed immediately and appropriate treatment measures should be employed. Patients should also be reminded to store transdermal drug patches in their original packaging and keep in a cool, dry place until they are ready to be used.

References

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