DEET - Insect Repellant Toxicity

Introduction

DEET (N,N-diethyl-3-methylbenzamide) was developed by the military as an insect repellent in 1946 and introduced forpublic use in 1957.1 It has broad-spectrum activity and effectively repels most mosquitoes, biting flies, chiggers, fleas and ticks. It is the most effective insect repellent available for human use.2 Currently, DEET is formulated in aerosols, pump sprays, lotions, creams, liquids, sticks, roll-ons and impregnated towelettes, with concentrations ranging from 5% to 100%. There is widespread use of products containing DEET due to the increasing incidence of West Nile Virus in the United States and recommendations by the Centers for Disease Control that it is the preferred insect repellant. It is estimated that 30% of the population in the United States applies DEET each year.1 The widespread use, concern for mosquito-born viruses, and media attention, have rekindled interest in DEET and its potential toxicities.3

Pharmacology/Pharmacokinetics

DEET is absorbed through the skin. Dermal absorption depends on the concentration and solvents in the formulation. In one study, an average of 5.6% of the total dose was absorbed following the dermal application of 100% DEET. After application of 15% DEET in ethanol, the average absorption was 8.4%. Systemic absorption began within two hours of topical application.4 Dermal absorption of DEET may also vary by age and body mass. Infants less than 2 months of age have a larger surface area to body mass ratio and can more easily attain elevated plasma concentrations. Absorption can also be increased when DEET is applied to broken skin. When DEET is formulated with ethanol, absorption may also be increased as ethanol enhances permeability of the skin.3,4 Absorption decreases under conditions of perspiration and elevated body temperature.2 DEET distributes into skin and fatty tissues but does not accumulate in the superficial layers of the skin. Following removal of DEET from the surface of the skin, the remaining product in the lower layers of the dermis is absorbed, metabolized and excreted in the urine. The rate of elimination of DEET after topical application is faster than the rate of absorption, and elimination has been found to be complete within 12 hours of removal. Six main metabolites, none of which are known to be toxic, have been isolated in human urine, however two metabolites predominate. DEET undergoes oxidation by cytochrome P450 2B6 and 1A2 to form N, N-diethyl-m-hydroxymethylbenzamide, while dealkylation by cytochrome P450 2C19 and 3A4 forms Nethyl-m-toluamide. The primary route of elimination is through the urine, with negligible elimination in the feces.4 The metabolism of DEET may change in response to large exposures; more of the parent compound is excreted unchanged in the urine and several additional metabolites may be present in the urine.3 The concentration of DEET and the protection time it provides are directly related, although the protection time reaches a plateau when the concentration approaches 50%. Controlled-release formulations do not prolong the time of protection, but alcohol-based formulations have been shown to increase time of protection.2 There is little information available about oral absorption. Severe symptoms have appeared within 30 minutes of ingestion, which implies rapid GI absorption.

Adverse Effects

DEET has few adverse effects when applied as directed. The most common problem is local skin irritation, including erythema and pruritis, at the site of application. One case of anaphylaxis after brief exposure to DEET has been reported.1 When the patient was re-exposed to DEET in an emergency department she experienced similar symptoms of anaphylaxis. Many people, including military and forest service personnel, apply high concentrations of DEET on a daily basis and have developed more severe adverse effects due to chronic exposure. These adverse effects included insomnia, muscle cramps, mood disturbances and rashes.1

Clinical Toxicology/Toxicokinetics

The toxicity of DEET is largely dependent upon the route of exposure and dose. The most common unintentional route of exposure is ocular as many DEET formulations are sprays or liquids.5 DEET causes local irritation and discomfort when introduced into the eyes or oral cavity.6 DEET has not been shown to cause severe, long-term damage to the eye in animals.7 Ingestions of DEET have been associated with nausea, vomiting, hypotension, encephalopathy, seizure, coma, and ataxia.6 Ingestion of 50 mL of 100% DEET by a 33 year-old woman resulted in hyptotension, coma, seizures and death. Ingestion of 25 mL of 50% DEET by a one-year-old child resulted in coma and seizures.8 Small ingestions of DEET, such as unintentionally spraying the product into the mouth, usually do not cause toxic effects. Excessive dermal application of DEET to large areas of the body over a period of days to weeks, especially in children, has led to seizures, bradycardia, nausea, vomiting, bullous eruptions, lethargy, ataxia, encephalopathy and anaphylaxis.6 Neurotoxicity is the most commonly reported systemic toxic effect of DEET and the mechanism is unknown. It has been suggested that DEET may induce neuronal apoptosis or disrupt the permeability of the blood-brain barrier, but neither of these hypotheses have been proven.3 There are multiple case reports describing seizures after exposure to DEET but many of these cases have few details and too many confounding variables to establish absolute causation.1 While the majority of reports involve large exposures, there are several reports of seizures following brief exposures to DEET. One case report of seizure following a brief exposure involved a normally healthy 5 year-old boy who applied DEET over his entire body in the form of Muskol® (95% DEET) in the morning and Off® (unknown DEET concentration) later on in the day. The boy experienced a seizure, which was successfully treated with diazepam, and respiratory arrest, which was managed by intubation and ventilation. He recovered without sequelae.9

Pregnancy/Lactation Issues

Animal studies have not shown DEET to be a teratogen even after long-term use. A study performed in Thailand on pregnant women in their second and third trimesters using DEET as malaria protection showed no difference in adverse effects on mother or child between the DEET and placebo group.10 DEET can cross the placenta when used long-term, but the exposure to the fetus has not proven to be significant. 3,10 The CDC recommends that DEET should be used in pregnant and lactating women to protect themselves and their fetus from potentially life-threatening diseases carried by mosquitoes and other vectors.3

Treatment

Treatment of DEET exposure consists of decontamination and supportive care. Up to 85% of DEET exposures reported to the American Association of Poison Control Centers between 1993-1997 were managed on-site in a non-health care facility.11 After ocular exposure the eyes should be irrigated from the eye with lukewarm water for 15 minutes. Patients with persistent eye irritation or pain should be evaluated for corneal injury or chemical conjunctivitis. Following large dermal exposure, the area should be washed 2-3 times with soap and water or an alcohol-detergent solution such as “green soap”. Inducing emesis is not recommended, but gastric aspiration via nasogastric tube followed by activated charcoal may be of benefit if large quantities are ingested and the patient presents within one hour of ingestion. Ingestion or dermal application of DEET rarely causes seizures, but when seizures occur diazepam or another benzodiazepine should be utilized. Other supportive therapies such as anti-emetics for nausea and vomiting, intravenous fluids and vasopressors for hypotension, and antihistamines for severe skin irritation may be useful. There is no specific antidote available for treatment of DEET toxicity.

Summary

Approximately 30% of the population applies DEET as protection against West Nile Virus and other mosquito-born viruses and the number of toxic exposures associated with DEET is extremely low in relation to the large number of people who apply it.1,5,11 Many exposures lead to mild irritation of the skin or eyes and can be managed at home.5,11 The neurotoxicity associated with DEET is rare but may occur with large exposures.3 Treatment consists of decontamination and supportive care. DEET is safe to use as directed in the general public, including pregnant and lactating women as well as children 2 months and older.3,10

Recommended Application Guidelines 12,13

- Apply DEET product only when planning to be outdoors in a mosquito-infested area.
- Use the appropriate concentration of DEET. Children and adults in the general public should use 30% or less. A product with a concentration of 10% or less may be more appropriate for children under 12 years.
- Do not apply DEET to children under 2 months of age.
- When using on children, apply to your own hands and then put it on the child.
- Do not apply to children’s hands.
- Do not allow children to handle products containing DEET.
- Do not apply over cuts, wounds, or irritated skin.
- Do not apply near eyes and mouth. Apply sparingly around ears.
- Reapply DEET only as directed by packaging. The effective duration depends on the concentration of DEET in product.
- Use just enough repellent to cover exposed skin/and or clothing.
- Do not use on skin under clothing.
- Avoid over-application of DEET products.
- After returning indoors, wash treated skin with soap and water.
- Wash treated clothing before wearing it again.
- Do not apply a combination product containing sunscreen and DEET.

- Do not spray aerosol or pump products in enclosed areas.
- Do not apply aerosol or pump products directly to your face. Spray your hands and then rub them carefully over the face, avoiding eyes and mouth.

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