Toxic encephalopathy associated with use of DEET insect repellents: a case analysis of its toxicity in children

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(1) Respiratory distress and seizures developed in an 18-month-old boy following brief exposure to low-strength (17.6%) N,N-diethyl-m-toluamide (DEET). A review of the literature revealed 17 reports of DEET-induced encephalopathy in children. The objective of this study was to test the hypothesis that the potential toxicity of DEET is high and that available repellents containing DEET, irrespective of their strength, are not safe when applied to children’s skin. (2) Although this is a case report, we used the features of published reports of DEET-induced encephalopathy in children to support the diagnosis, since the evidence that the child’s illness was caused by DEET was circumstantial. In the following case analysis, clinical reports of children < 16 years old have been reviewed and analyzed in an effort to relate direct DEET toxicity to various clinical, demographic, and toxic compound exposure factors (Fisher’s exact test and logistic regression analysis). (3) DEET-induced encephalopathy in children (56% girls) followed not only ingestion or repeated and extensive application of repellents, but also a brief exposure to DEET (45%). Of those who reported a dermal exposure, 33% reported an exposure to a product containing DEET < 20%. Seizures, the most prominent symptom (72%), were significantly more frequent when DEET solutions were applied to the skin (P < 0.01). Mortality (16.6%) did not correlate significantly with the concentration of the DEET liquid used, duration of skin exposure, pattern of use, age, or sex. (4) Data of this case analysis suggest that repellents containing DEET are not safe when applied to children’s skin and should be avoided in children. Additionally, since the potential toxicity of DEET is high, less toxic preparations should be probably substituted for DEET-containing repellents, whenever possible. Human & Experimental Toxicology (2001) 20, 8–14.

Keywords: N,N-diethyl-m-toluamide; DEET; insect repellents; toxic encephalopathy; seizures; children

Introduction

N,N-diethyl-m-toluamide (DEET) is the most commonly used mosquito repellent. Although it is effective and has occasionally been used by millions, in recent years, there have been a number of reports of serious reactions, some fatal, to DEET. Ingestion of DEET rapidly caused convulsions, severe hypotension, respiratory depression, coma, and death. Variable and unpredictable toxicity related to DEET application has also been previously reported in the literature. When concentrated solutions were applied to the skin, there was a possibility of systemic toxicity causing urticaria, skin necrosis, anaphylaxis, cardiovascular toxicity, and manic psychosis.

The DEET transdermal bioavailability and mean absorption time of a commercial lotion were 18.3% and 2.05 h, respectively. In adults, DEET is absorbed through the skin and 9% of an applied dose is absorbed over 12 h, whereas 10–14% of the administered dose is excreted unchanged in the urine in the first hour. DEET is oxidized by hepatic microsomes, and metabolites can persist in skin and fatty tissues for 1 or 2 months. Experimental studies have also demonstrated the possibility of harmful effects on gonads and embryos. Adults, as well as children, are at risk for direct toxicity from DEET. However, the metabolism and elimination characteristics have not been studied in children, who have very much thinner skin and greater surface area:mass ratio. It has been recommended that only dilute DEET should be applied to children. Our interest in this subject arose from a case of encephalopathy in an 18-month-old boy following topical use of 17.6% DEET. We reviewed published reports of children in whom...
encephalopathy developed following exposure to DEET (MEDLINE Search) and analyzed the findings (case analysis).

Materials and methods

Case report
An 18-month-old boy, who had been previously healthy, presented to a community health center of a small island with generalized seizures and respiratory difficulties. His parents, who were street vendors, had come to the island 3 days ago to trade. That morning, the child was noted to be drowsy, irritable, and vomiting. Soon he had generalized convulsions and respiratory difficulty and was rushed to the health center. More seizures were witnessed there and he was given diazepam rectally and a loading dose of phenytoin intravenously. Pupils were equal and reactive to light. There was no focal neurologic deficit and the eye grounds were normal. He continued to have generalized seizures and respiratory difficulties. His pulse rate was 110 beats/min and SaO₂ was 72%. He became comatose and responded only to painful stimuli. His trachea was intubated and mechanical ventilation was instituted. Following intubation and stabilization, the patient was transferred to our institution for further management.

Family history was negative, with no evidence of seizure disorder or other neurologic disease. The other family members were well. Patient's development was normal until this episode. Immunizations were up-to-date. Past medical history was uncontributory. There was no history of seizures, trauma, or other childhood illness. However, the family had camped in the countryside and last night, because mosquitoes were numerous about the tent, the child had been applied with Autan, an insect repellent, containing 17.6% DEET (Bayer AG, Germany).

On arrival, his pulse rate was 160 beats/min, his blood pressure 100/60 mm Hg, and temperature 37°C. He was hypertonic with intermittent opisthotonic spells. Pupils were equal and reactive to light. There were no rashes. A chest roentgenogram and an electrocardiogram were normal. Admission biochemical and blood tests were unremarkable. Calcium, urea nitrogen, creatinine, and ammonia were normal. Arterial blood gases were normal (pH 7.37, pO₂ 19 kPa (144 mm Hg), pCO₂ 4.8 kPa (36 mm Hg), HCO₃ 18 mmol/l, SaO₂ 99%). Blood specimens revealed a leukocyte count of 10.4 × 10⁹/l (56% neutrophils, 36% lymphocytes, 8% monocytes). The cerebrospinal fluid (CSF) had normal levels of protein <20 mg/dl, glucose 50 mg/dl, and two cells. Blood and CSF cultures for bacteria and fungi yielded no microorganisms. Virus titer determination in the serum and polymerase chain reaction of blood samples for the detection of viral genome were negative, as were mycoplasma titers. The laboratory investigation of metabolic disease was also negative. The child's electroencephalogram (EEG) had slow background activity without discharges (postictal). Computed tomography scan (CTS) of the brain was normal.

Next day, the patient was extubated. He was responsive and alert and neurologically normal.

The following 7 days in the hospital were uneventful, after which he was discharged home. EEG after a week was normal, and the child remained normal. The clinical signs of toxicity, along with the thoroughly negative work-up and the positive history of the preceded repelled exposure, oriented the diagnosis to the DEET toxicity. The patient was followed in the outpatient clinic and continued to do well. He continued to be well 9 months after the initial illness.

Material for case analysis
A literature search in MEDLINE revealed reports of 17 children, younger than 16 years old, in whom encephalopathy developed following exposure to DEET. Clinical and demographic data of these cases are summarized in Table 1.

Statistical analysis
Fisher's exact test was used for the category data. Logistic regression analysis was used to analyze the contribution of the various exposure factors, product variables, and the patients' demographic data to the outcome. All analyses were done using the Statistical Package for the Social Sciences for Windows (release 8.0, SPSS, Chicago, IL) software package.

Results
Eighteen children (mean age 7.5 + 4.7 years) with DEET-induced encephalopathy, from 12 reports from six countries, entered the study; 28% of the cases occurred in children under 2 years old. The proportion of boys to girls was 7:10 (girls 56%).

Both oral and cutaneous routes of administration were implicated (Table 1). Of the 18 cases, 13 (72%) involved dermal exposure and five oral exposure. Of those who reported a dermal exposure, 22% reported an exposure to a product containing DEET <16%; 33% of the patients reported an exposure to a product containing DEET <20%. In the remaining patients, the concentration of DEET was either mixed or >20%. The duration of skin exposure varied from a brief pattern of hours (17%) or <3 days (28%), to a repeating one from 10 days to 3-month duration.

All patients were reported to have experienced serious effects from the exposure and three died
Table 1 Reported cases of DEET-induced encephalopathy in children

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Percent DEET used</th>
<th>Pattern of use</th>
<th>Route</th>
<th>Symptoms</th>
<th>Laboratory</th>
<th>Outcome</th>
<th>Possible alternative diagnosis</th>
<th>Country</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>M</td>
<td>17.6</td>
<td>Brief (hours)</td>
<td>Cutaneous</td>
<td>Seizures, opisthotonus, respiratory difficulty, coma, agitation</td>
<td>CSF: normal, CTS: normal</td>
<td>Recovery</td>
<td>None</td>
<td>Greece</td>
<td>PR</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>F</td>
<td>10</td>
<td>Nightly ×3 months</td>
<td>Cutaneous</td>
<td>Seizures, opisthotonus</td>
<td>CSF: WBC = 165</td>
<td>Death</td>
<td>Encephalitis, parainfectious encephalopathy</td>
<td>South Africa</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>F</td>
<td>10</td>
<td>Small</td>
<td>Oral</td>
<td>Agitation, opisthotonus</td>
<td>CSF: WBC +</td>
<td>Recovery</td>
<td>Encephalitis, parainfectious encephalopathy</td>
<td>South Africa</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>3.5</td>
<td>F</td>
<td>15</td>
<td>Daily ×2 weeks 50 ml</td>
<td>Cutaneous</td>
<td>Seizures, coma, hypotension, hypertonia</td>
<td>CSF: normal, NA</td>
<td>Recovery</td>
<td>None</td>
<td>United States</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>F</td>
<td>95</td>
<td>Oral</td>
<td>Cutaneous</td>
<td>Seizures, coma, opisthotonus</td>
<td>NA</td>
<td>Recovery</td>
<td>Idiopathic seizure</td>
<td>Canada</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>F</td>
<td>47.5</td>
<td>Oral</td>
<td>Oral</td>
<td>Seizures, hypertension, opisthotonus</td>
<td>NA</td>
<td>Recovery</td>
<td>None</td>
<td>Canada</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>F</td>
<td>95</td>
<td>Brief (2 days) 50 ml</td>
<td>Cutaneous</td>
<td>Rash, seizures, altered behaviour with unusual restlessness, agitation</td>
<td>NA</td>
<td>Recovery</td>
<td>None</td>
<td>Canada</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>F</td>
<td>15 and 100</td>
<td>Brief (2 days) 50 ml</td>
<td>Cutaneous</td>
<td>Ataxia, bizarre movements, drooling, opisthotonus, oculomotor, myoclonus, tremors</td>
<td>CSF: WBC 14, CTS: normal</td>
<td>Recovery</td>
<td>Encephalitis, parainfectious encephalopathy, myoclonic encephalopathy</td>
<td>United States</td>
<td>15</td>
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<tr>
<td>9</td>
<td>1.5</td>
<td>F</td>
<td>20</td>
<td>Daily ×3 months</td>
<td>Cutaneous</td>
<td>Seizures</td>
<td>CSF: normal, hyperammonemia</td>
<td>Death</td>
<td>Reye syndrome or congenital OCT deficiency</td>
<td>Canada</td>
<td>38</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>F</td>
<td>15</td>
<td>10 occasions</td>
<td>Cutaneous</td>
<td>Seizures</td>
<td>CSF: normal, hyperammonemia</td>
<td>Death</td>
<td>Acute encephalopathy of unknown origin</td>
<td>Uruguay</td>
<td>17</td>
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<tr>
<td>11</td>
<td>1.4</td>
<td>F</td>
<td>10 or 20</td>
<td>Daily ×3 weeks</td>
<td>Cutaneous</td>
<td>Seizures</td>
<td>CSF: normal, CTS: normal</td>
<td>Recovery</td>
<td>Idiopathic seizures</td>
<td>United States</td>
<td>40</td>
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<tr>
<td>12</td>
<td>5</td>
<td>M</td>
<td>100 and 15</td>
<td>Brief (hours)</td>
<td>Cutaneous</td>
<td>Seizures</td>
<td>CSF: normal, CTS: normal</td>
<td>Recovery</td>
<td>None</td>
<td>United States</td>
<td>26</td>
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<td>13-16</td>
<td>3-7</td>
<td>M</td>
<td>Varying</td>
<td>Brief (&lt;3 days)</td>
<td>Cutaneous</td>
<td>Seizures</td>
<td>CSF: normal, CTS: normal</td>
<td>Recovery</td>
<td>None</td>
<td>United States</td>
<td>26</td>
</tr>
<tr>
<td>17</td>
<td>15</td>
<td>M</td>
<td>NA</td>
<td>Brief (&lt;3 days)</td>
<td>Cutaneous</td>
<td>Seizures, urticaria</td>
<td>MRI: normal</td>
<td>Recovery</td>
<td>None</td>
<td>United States</td>
<td>41</td>
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<tr>
<td>18</td>
<td>8</td>
<td>NA</td>
<td>30 or &gt;30</td>
<td>Brief (hours)</td>
<td>Cutaneous</td>
<td>Seizures, respiratory depression, toxic hepatitis</td>
<td>NA</td>
<td>Recovery</td>
<td>None</td>
<td>United States</td>
<td>42</td>
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</table>

*NA = not available; PR = present report; **OCT = ornithine carbamoyl transferase.
Only patients with cutaneous exposure died; mean age, sex, or duration of skin exposure did not differ significantly between survivors and non-survivors. Logistic regression analysis showed that mortality did not correlate with the concentration of the DEET liquid used, the duration of skin exposure, or the pattern of use.

The most common symptoms reported were convulsions (72%), coma (39%), behavioral changes (28%), opisthotonus or hypertonia (22%), and ataxia (17%). Less frequently reported symptoms were respiratory difficulty (11%), hypotension (11%), and hepatitis or Reye-like syndrome (5.5%). Seizures were significantly more frequent when DEET solutions were applied to the skin (P<0.01), whereas coma was more frequent after ingestion of DEET (P<0.05). Other symptoms, as they appear in literature, did not differ significantly between children exposed to DEET through the oral or the cutaneous route (Figure 1).

In only three cases, the CSF showed lymphocytosis (14 cells in one report) and/or high levels of protein. In one case with normal CSF, EEG was abnormal, whereas only one patient was reported with hyperammonemia. When reported, CTS and magnetic resonance imaging (MRI) images were normal. Overall, normal laboratory findings were reported in eight cases (44%). Laboratory data were not available in 28% of reports. There were no alternative diagnoses in 56% of the reports. Idiopathic seizures (22%) or encephalitis (22%) were the main alternative diagnoses presumed, which, however, could not be adequately supported. A case of a possible interaction of DEET with the urea cycle has also been reported.

**Discussion**

In this series, toxic encephalopathy in children has followed not only repeated and extensive administration, but also brief application of up to 10% DEET. In particular, the patient who is being discussed had toxic encephalopathy after a brief dermal exposure to DEET, a widely used insect repellent. Applied to the skin, DEET is the active agent in most insect repellents, such as various mosquitoes, ticks, fleas, quats, biting flies, and chiggers. It is sometimes combined with other repellents such as ethohexadiol and dimethylphthalate. It is marketed in concentrations from 5% to 100% as liquids (usually with ethanol or isopropanol), aerosols, pump sprays, lotions/creams, roll-on sticks, and impregnated towelettes.11

In humans, DEET has both local and systemic toxic effects; local effects include dermatitis, ranging from
erythema to bullous eruption.\textsuperscript{12} DEET produced similar lesions in a group of adult volunteers.\textsuperscript{13} Additionally, episodes of confusion, irritability, and insomnia have been reported by Everglades National Park employees following repeated and prolonged use of DEET.\textsuperscript{14} Coma, convulsions, respiratory failure, hypotension, and death can also occur, particularly after ingestion or dermal exposure to large amounts.\textsuperscript{15} Ingestion of DEET rapidly causes coma, convulsions, severe hypotension, and respiratory depression; the case fatality may be as great as 40%.\textsuperscript{2} What is important in this series is that similar symptoms were noticed between children exposed to DEET through the oral or the cutaneous route — the latter related to deaths — thus underlining the potential toxicity of both routes. Our patient presented with respiratory difficulty, seizures, and coma. Seizures were the most common symptom in the patients entered in this study, especially after cutaneous exposure. Ataxia, coma, and opisthotonus were also frequently encountered among children with encephalopathy associated with use of DEET. Finally, slurred speech, staggering gait, agitation, tremors, and death resulted.\textsuperscript{16-19} At autopsy, edema of the brain, as well as congestion of the meninges, was found.\textsuperscript{20}

The dose relationship between DEET exposure and the symptoms reported in the clinical literature is difficult to establish.\textsuperscript{32} It has been presumed that intoxication of DEET may occur after repeated applications of high-strength compounds.\textsuperscript{21,22} Our patient had been exposed to an ethanolic solution of 17.6% DEET concentration. Other children in this case analysis had developed toxic encephalopathy after cutaneous exposure to either dilute DEET of 10%,\textsuperscript{23} 15%,\textsuperscript{18,21,24} or 20%,\textsuperscript{17,25} or to repellents containing higher or unknown concentrations of DEET.\textsuperscript{26} In our country, insect repellents for human use based on DEET are in the form of lotion, stick, and spray in concentrations between 9.6% and 20%. However, whatever concentration of alcoholic solution is applied, the solvent will presumably evaporate to leave concentrated DEET on the skin.\textsuperscript{27} Even parents applying on their children’ skin preparations that contain lower concentrations are likely to apply larger volumes to obtain the desired insect repellency. Although only 3–8% of the DEET applied to the adult forearm skin is absorbed\textsuperscript{28} over 12 h, the range of skin absorption at different conditions of heat or moisture is not known.\textsuperscript{29} It is known, however, that because DEET is partially absorbed through the skin, it has been used to enhance dermal delivery of other drugs.\textsuperscript{29} In an experimental study, it has been shown that in the monkey, 68% of DEET is absorbed from the ventral forepaw, a site corresponding to the human palmar surface.\textsuperscript{19} In another study, which has been conducted across human skin, it was shown that there is potential for significant absorption of DEET after dermal application of commercial mosquito repellents, since ethanol, used as a solvent, may significantly enhance the permeation of DEET.\textsuperscript{30}

Thus, the total amount of DEET permeated from 30–45% ethanolic solutions at the end of 36 h was significantly higher than that from pure DEET. Even in adults experimentally receiving the same DEET dose, peak concentrations differed by as much as 3–5\textsuperscript{2}. Thus, for safety concerns, the incorporation of ethanol in commercial DEET products needs to be reevaluated. Especially, the topical formulation vehicle based on PEG 400, Carbowax 940NF, and Pemulen TR-2 was effective in reducing DEET skin permeation.\textsuperscript{32} Similarly, a new insect repellent formulation, a PEG–polyacryl acid polymer system, for its DEET release, exhibited reduced in \textit{vitro} skin permeation and \textit{in vivo} transdermal absorption of DEET as well as superior repellency compared with a commercial DEET lotion.\textsuperscript{33} Furthermore, it was shown that the bioavailability of DEET from 10% ethanol solution was 45%, whereas the bioavailability of DEET from liposomes was 16%, a threefold reduction in the amount of DEET absorbed.\textsuperscript{34} Although all of the absorbed drugs are metabolized, urinary DEET and ethyltoluamide (a metabolite) levels peaked at 8 h and were still detectable 48 h after treatment.\textsuperscript{35}

Being lipid-soluble, DEET accumulates in the brain.\textsuperscript{2} There is a remarkably close similarity of the structure of DEET and nikenamide — a convulsant\textsuperscript{5} — which may explain why in this series seizures appear to be present in 72% of the cases of DEET encephalopathy in children. In a recent experimental study, an acute toxic interaction has been described in which sublethal doses of DEET induced seizures that were resistant to standard anticonvulsants.\textsuperscript{36} DEET appeared to operate through different mechanisms from other toxic agents to produce seizures. In 72% of patients in this case analysis, laboratory findings were either normal or unavailable (unremarkable?). There were no alternative diagnoses in 50% of the reports. Idiopathic seizures (22%) or encephalitis (22%) were the main alternative diagnoses presumed, which, however, could not be adequately supported. We suggest that pediatricians evaluating patients with unexplained seizures should consider the possibility of exposure to DEET.

Our patient, like the patients of Roland \textit{et al}.\textsuperscript{18} Gryboski \textit{et al},\textsuperscript{23} Heick \textit{et al},\textsuperscript{38} and Lipscomb \textit{et al},\textsuperscript{30} and in contrast to the patients described by Zadikoff,\textsuperscript{20} had normal CSF. He was afebrile, had normal (initially postictal) EEG, and did not have hyperammonemia, contrasting previous reports implicating febrile seizures,\textsuperscript{24} or ornithine carbamoyl transferase deficiency in the pathogenesis of DEET.
toxicity. In a patient who was a heterozygote for ornithine carbamoyl transferase, neither the effect of DEET on the urea cycle, nor the effect of chronic dilantin therapy on DEET metabolism could be excluded. Interestingly, phthalyl alcohol, which has a structure similar to DEET, was found in this patient’s liver at least 10 days after administration. In our patient, the illness ran a self-limited course once the toxic agent was removed. Similarly, in experimental studies, those animals that survived the systemic effects recovered completely. An interesting finding of this series, however, is that DEET-induced encephalopathy in children followed not only the repeated and extensive application of repellents, but also a brief exposure to DEET. In particular, our small patient experienced seizures up to 12 h after unique application of DEET. Two more cases developed acute encephalopathy following only some hours of skin exposure to DEET. Additionally, another five children developed acute encephalopathy following 1 or 2 days of skin exposure to DEET. It seems, therefore, that children or a more sensitive subset thereof appear to be more susceptible to direct DEET neurotoxicity than adults. We hypothesize that ethanol, a DEET solvent, may enhance the permeation of DEET in children significantly more than the permeation of pure DEET in adults, probably because of their thinner skin and greater surface area:mass ratio. This is further supported by reports showing that the deaths occurring from dermal application have been only in children. Mortality in this series of children with encephalopathy following exposure to DEET reached 16.6%. And, surprisingly, it did not correlate with the concentration of the DEET liquid used, the duration of skin exposure, or the pattern of use. Although it is not clear in this series, peripheral muscarinic receptors might have played a specific role in lethality caused by DEET.

The data on DEET toxicity in children, who have always been the “therapeutic orphans”, are still incomplete, since the metabolism and elimination characteristics have not been studied in children and infants. Accordingly, like all other drugs, DEET-based insect repellents should be tested, along with the enhancement effect of various solvents, in children regardless of the regulating agency. Careful toxicologic and epidemiologic studies must be conducted, including adequate documentation of DEET levels in affected and unaffected persons. Meanwhile, data of previous reports along with our case suggest that use of available repellents containing DEET may not be safe when applied to children’s skin and should be avoided in infants and young children. Especially, our analysis shows that the broad-spectrum topical insect repellent DEET is highly skin permeable, and serious adverse effects associated with the use of commercial DEET products may occur in children due to extensive DEET skin permeation. Additionally, since the potential toxicity of DEET is high, less toxic or new insect repellent formulations should be probably substituted for DEET-containing repellents or their current topical formulation vehicles, whenever possible.

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