Poisoning from dermal absorption of promethazine

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Two cases in which dermal absorption of promethazine hydrochloride resulted in a toxic neurologic syndrome are reported. The symptoms included central nervous system depression, acute excitomotor manifestations, ataxia and visual hallucinations. In addition, peripheral anticholinergic effects occurred. These symptoms are comparable with those of oral, intramuscular and rectal overdose of promethazine. The demonstrated risks of the topical use of promethazine outweigh any benefits.

On signale deux cas dans lesquels l'absorption dermique de chlorhydrate de prométhazine a entraîné un syndrome neurologique toxique. Les symptômes comprenaient une dépression du système nerveux central, des manifestations excitomotrices aiguës, l'ataxie et des hallucinations visuelles. De plus, on a noté des effets anticholinergiques périphériques. Ces symptômes sont comparables à ceux d'un surdosage à la prométhazine par voie orale, intramusculaire ou rectale. Les risques démontrés de l'usage topique de la prométhazine emportent sur tout avantage.

Phenergan cream 2% (2% promethazine cream) is a nonprescription antihistaminic marketed in Canada and Europe. The product label states that the cream is for "relief of itching due to insect bites or poison ivy, minor burns, mild skin irritation" and instructs the consumer to apply as required. Although the package label warns against "prolonged exposure to sun rays after application", there is no caution regarding systemic toxicity following dermal absorption. We report two cases in which dermal absorption of promethazine hydrochloride resulted in a toxic neurologic syndrome.

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Case reports

Case 1

A healthy 44-month-old girl weighing 15.5 kg was treated for pruritus associated with mild atopic eczema with a therapeutic oral dose (10 mg) of hydroxyzine syrup. One hour later 10 to 15 g of Phenergan cream 2%, containing 200 to 300 mg (12.9 to 19.4 mg/kg of body weight) of promethazine, was applied sparingly to the skin of her abdomen and proximal anterior thighs (approximately 13% of her total body surface area). The axillae and the perineal area were spared. Three hours later she awoke screaming and was taken to the emergency department.

The patient had no history of ingestion of promethazine cream or other drugs. She was mumbling incoherently and experiencing visual hallucinations. Her temperature was 36°C, her pulse rate was 76 beats/min, her respiratory rate was 20/min, and her blood pressure was 96/60 mm Hg. Her pupils were dilated and reacted slowly to light. The mucous membranes of her mouth were dry. Eczema was present on her face, trunk and extremities, but no obvious breaks of her skin were noted.

The girl was bathed with soap and water and admitted for observation. Six hours after admission she was given 5 mg of diazepam orally because of increasing excitomotor symptoms and screaming and the persistence of the visual hallucinations. Twelve hours after admission her behaviour returned to normal. She did not void until 15 hours after application of the promethazine cream. Thin-layer chromatography of the urine documented the presence of promethazine and not hydroxyzine. No other antihistaminics or psychotropic agents were identified.

Case 2

A 16-month-old boy weighing 11 kg was well except for mild atopic eczema and pruritus. On the day of admission to hospital his mother applied approximately 15 g of Phenergan cream 2%, containing 300 mg (26 mg/kg of body weight) of promethazine, to the skin of his head, trunk and extremities (approximately 30% of his total body surface area). The axillae and the perineal area were spared. Within 30 minutes he fell asleep, and on awaking 2 hours later he was irritable and ataxic and did not appear to recognize his mother. He was brought to the emergency department 8 hours after application of the promethazine cream.

The patient had no history of ingestion of promethazine cream or other drugs. He was irritable, agitated and intermittently drowsy. His temperature was 37.4°C, his pulse rate was 164 beats/min, his respiratory rate was 40/min, and his blood pressure was 120/78 mm Hg. He had mild generalized eczema but no obvious breaks of his skin.

Initial treatment consisted of bathing with soap and water. The boy was then admitted for observation and further evaluation. The leukocyte count was 8.3×10^9/L. The serum electrolyte, blood sugar and serum calcium levels were normal. Lumbar puncture revealed a slightly turbid fluid with a leukocyte count of 2×10^6/L, an erythrocyte count of 2080×10^6/L and a normal glucose concentration. Cultures of the cerebrospinal fluid and peripheral blood were sterile. Urine was not obtained from the first voiding after application of the promethazine cream. Thin-layer chromatography of the urine obtained from the second voiding, 10 hours after application of the promethazine cream, did not identify promethazine; the limit of detection of promethazine was low (approximately 1 μg/mL). No other antihistaminics or psychotropic agents were identified.

Twelve hours after application of the promethazine cream the patient's condition was markedly improved, and by 18 hours the boy was asymptomatic.

Discussion

Promethazine is a phenothiazine with histamine-H_1-receptor blocking activity and anticholinergic activity. Drugs with anticholinergic properties can produce a toxic confusional state, thought to be due in part to the inhibition of central neurotransmitter activity.

Oral doses of promethazine reported to have produced toxic effects range from 6.7 to 28 mg/kg of body weight.[1,2] Our patients received topical doses of 12.9 to 26 mg/kg. Although the bioavailability and pharmacokinetics of promethazine following dermal application are unknown, it is conceivable that dermal overdose could result in dystonic crisis,[3] respiratory arrest[3,4] or death.[5]

Our patients exhibited a toxic neurologic syndrome that included central nervous system depression, disorientation, inability to recognize the parents, irritability, screaming, incoherent speech, ataxia, visual hallucinations and acute excitomotor manifestations. In addition, peripheral anticholinergic effects, including mydriasis, xerostomia and tachycardia, were seen. These symptoms and signs are comparable with those of oral,[1-3] intramuscular[4] and rectal[6] overdose of promethazine.

In case 1, 10 mg of hydroxyzine had been given 1 hour before the promethazine was applied and may have contributed to the initial effects. However, we do not feel that hydroxyzine was responsible for the prolonged toxic neurologic symptoms for the following reasons: the dose of hydroxyzine was within the therapeutic range; hydroxyzine has a plasma elimination half-life of 3 to 4 hours,[7] whereas the symptoms and signs in this case increased over 10 hours; and hydroxyzine was not identified in the urine by thin-layer chromatography, although it was specifically sought. Certainly the features of this case suggest that promethazine was the etiologic agent.

In case 2 the topical application of promethazine and the onset of symptoms in the absence of other agents or disease strongly support the contention that topical promethazine caused the toxic neurologic syndrome. The negative result of thin-layer chromatography of the urine from the second voiding could have been expected since the specimen was not optimal.

Initial management of patients with promethazine intoxication should include symptomatic supportive care of the cardiovascular and respiratory systems. In cases of dermal exposure the skin must be cleansed to remove any unabsorbed intoxicant. Although pharmacologic antagonism of the anticholinergic effects of promethazine has been accomplished by intravenous administration of physostigmine,[2] this drug has been associated with undesirable effects[8] and should not be used routinely.

Physicians must be aware that topical administration of promethazine may result in a toxic neurologic syndrome. In addition, the topical use of phenothiazines may cause photosensitization as well as skin sensitization, with the subsequent development of contact dermatitis.[9,10] Clearly, the demonstrated risks of the topical use of promethazine far outweigh any benefits.

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