

CLINICAL OBSERVATION

Successful therapy of paediatric ethylene glycol poisoning: a case report and annual survey by a regional poison centre

Nicolaus Schwert¹, Herbert Desel², Manuela Schulz¹, Christina Schwert¹, Wieland Kiess¹, Werner Siekmeyer (Werner.Siekmeyer@medizin.uni-leipzig.de)¹

1.Hospital for Children and Adolescents, University of Leipzig, Leipzig, Germany

2.GIZ-Nord Poison Centre and Clinical Toxicology Laboratory, Georg-August-University Göttingen, University Hospital, Göttingen, Germany

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Correspondence

Werner Siekmeyer MD, Hospital for Children and Adolescents, University of Leipzig Oststraße 21-25 D-04103 Leipzig, Germany.
Tel: 49-341-9726-000 | Fax: 49-341-9726-009 | Email: Werner.Siekmeyer@medizin.uni-leipzig.de

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Abstract

Severe poisoning with ethylene glycol, often used as antifreeze, is a rare, life-threatening event. Neurological symptoms are accompanied by metabolic acidosis with elevated anion gap and osmotic gap.

We report on a 7-year-old boy suffering from severe ethylene glycol intoxication. Early diagnosis based on typical clinical signs and rapid initiation of specific therapy with ethanol resulted in complete and rapid recovery without haemodialysis becoming necessary. While one laboratory initially had not been able to detect ethylene glycol in the patient's blood, an ethylene glycol serum level of 3900 mg/L was measured by a second laboratory, the highest value ever reported in the scientific literature for paediatric cases. Ethylene glycol poisoning is verified by quantitative glycol analysis in serum, but only few laboratories are able to perform this investigation in emergency cases. Therefore, in the beginning diagnosis has to be based on patient's history and clinical signs. Every substantial suspicion of ethylene glycol poisoning has to be treated with an antidote (fomepizole or ethanol) immediately.

Conclusion: Ethylene glycol poisoning is rare in the paediatric age group in our series of glycol poisonings. One should keep in mind, that early diagnosis and treatment due to clinical signs is important and haemodialysis usually is not necessary.

The colourless and odourless liquid ethylene glycol (1,2-ethanediol, HO-CH₂-CH₂-OH) is used as antifreeze for car radiator fluids and other liquid car products. Furthermore, it is a constituent of many paints and disinfectants. Published data on the frequency of ethylene glycol poisonings vary widely: In 2004, 5816 cases with exposition to ethylene glycol, including 676 cases in children below 6 years and 869 cases in patients between 6 and 19 years had been reported in the United States. Twenty-two lethal cases were only seen in adults (1). Seven poisonings were reported for 2000 from a hospital in Canada (2). The GIZ-Nord Poison Centre (serving 13 million inhabitants in Northern Germany) has collected 38 documented human cases with exposition to ethylene glycol products in 2004, three of which had to be classified as (more than minor) intoxications (Table 1). As ethylene glycol ingestions are potentially hazardous events, they are challenging clinical paediatricians.

Table 1 Human ethylene glycol exposition cases in 2004 in Northern Germany (All data extracted from GIZINDEX case database of GIZ-Nord Poison Centre, Göttingen, Germany)

	n	No symptoms	Minor symptoms	Moderate symptoms	Severe symptoms	Death	No grading
Adults	20	12	2	1	1	1	3
1–4 years	12	12					
5–9 years	6	3	3				
Total	38	27	5	1	1	1	3

CASE REPORT

A 7-year old boy was found sitting alone on the ground at a forest's edge in early springtime. He responded to questions with blurred speech but could not explain the situation. Lowered body temperature and enuresis was detected. On arrival at the hospital the patient was cyanotic and comatose with slow and deep breathing. Heart rate was 150/min and blood pressure was 120/80 mmHg. Clinical investigation detected no further pathological findings. First laboratory blood results showed pH 7.10, pCO₂ 27.5 mmHg, bicarbonate (HCO₃⁻) 7 mmol/L, base excess -22 mmol/L, sodium (Na⁺) 152 mmol/L, potassium (K⁺) 5.4 mmol/L, calcium (Ca²⁺) 2.47 mmol/L, glucose 5.2 mmol/L, chloride (Cl⁻) 119 mmol/L, anion gap 26 mmol/L, and lactate 4.7 mmol/L. Normal results were reported for creatinine and urea, liver enzymes, prothrombin index, and other parameters of coagulation. Urine microscopy revealed numerous crystals of calcium oxalate type, but no cells and no protein.

Diagnosis and clinical course: After admission the patient showed polyuria (urine production 10 mL/kg/h). Based on this finding and laboratory results of metabolic acidosis with oxaluria glycol poisoning was suspected. Blood was sent to a regional toxicological laboratory for glycol analysis and intravenous antidote therapy with ethanol was started (0.6 g/kg within 60 min, followed by 0.1 g/kg/h). The patient showed sufficient spontaneous ventilation but blood pH did not change under treatment with hydrogen carbonate and salt solution (20 mL/kg/h) within 60 min. Therefore,

haemodialysis was set up. The primary diagnosis was strongly supported when police personnel found an empty antifreeze container close to the location where the patient had been discovered earlier. As pH returned to normal values, urine production decreased substantially and the patient awoke 2 h later (under continuation of the initial treatment). No haemodialysis was performed. 48 h after admission the boy was discharged from the intensive care unit with retrograde amnesia as the only remaining symptom. No pathological values for blood glucose and serum creatinine were detected at any time. Surprisingly, about 6 h after admission the toxicological laboratory reported that no ethylene glycol was to be detected in the patient's blood. As this result did not correspond to all other information collected in this case that far, a second laboratory was involved. Using a gas chromatographic separation technique and flame ionisation signal detection (3) ethylene glycol could be detected clearly in toxic concentrations. Serum level: 3900 mg/L ethylene glycol. Urine level: 13600 mg/L ethylene glycol (detection limit 8 mg/L, intraassay coefficient of variation 0.99987, according to DIN 32645).

DISCUSSION

Intoxication with ethylene glycol can be life threatening. Blood analysis on glycols is crucial for confirming the diagnosis but glycol analysis is rarely available rapidly enough for the selection of first line specific therapies in an emergency situation. Therefore, early treatment decisions are usually based on clinical signs and symptoms which are ethanol-like neurological symptoms (blurred speech, ataxia, somnolence, seizures), osmotic polyuria, urine microscopy with crystals of calcium oxalate type, metabolic acidosis with large anion gap, tachycardia, dysrhythmia, congestive heart failure, hyperreflexia, muscle spasms and potentially 24 to 72 h after ingestion renal damage with tubular necrosis, haematuria, proteinuria, oliguria, or anuria (4–6). Ethylene glycol itself does neither cause acidosis nor an increased anion gap but an increase of osmolality and therefore of osmotic gap. Unlike methanol poisoning the anion gap may be small even in major poisoning with ethylene glycol. This is due to the much greater molecular weight of ethylene glycol. The main cause of acidosis is dissociation of glycolic acid. Metabolites rather than ethylene glycol itself, are the main cause of toxicity. In the case reported here, severe metabolic acidosis with a large anion gap and increased lactate plasma level were observed. High osmolality stimulates diuresis with risk of hypovolemia and hypovolemic shock. Renal loss of hydrogen carbonate further increases acidosis. In one out of two cases calcium oxalate crystals are found in urine (4). Finding crystals may be a useful clue but they are not necessarily present. It is not possible to exclude ethylene glycol poisoning by lacking crystals. Several chromatographic methods for determination of ethylene glycol in serum have been published. Gold standard method for glycol identification is gas chromatography with mass selective detection (GC/MS) (7,8). A robust and rapid method for quantitative serum analysis of more than 15 glycols and glycol ethers using flame ionisation detection

Table 2 Criteria for antidotal therapy in ethylene glycol poisonings

- Ethylene glycol concentration in serum above 200 mg/L (3 mmol/L) or
- Patient's history of ingestion of a toxic dose of ethylene glycol and osmotic gap of more than 10 mosmol/kg or
- Suspicion of ethylene glycol poisoning by history or clinical signs and symptoms and two of the following criteria
 1. Arterial pH <7.3
 2. Bicarbonate in serum <20 mmol/L
 3. Osmotic gap > 10 mOsmol/kg
 4. Crystals of calcium oxalate in urine sediment

(GC/FID) was reported more recently (9,3). For hospital laboratories and even for specialised toxicology laboratories analysis of ethylene glycol is a rare enquiry. Only few laboratories are sufficiently equipped or prepared to carry out this analysis. On the other hand, a very quick availability of the test is crucial for initiating the therapy as fast as possible. Therefore analysis should be carried out only in reference laboratories that provide the test within 4 h on 24 h every day. It would be easier to manage the patients, if a greater number of reference laboratories could offer ethylene glycol and glycol acid analysis in this short turnaround time. There are no procedures for external quality control of glycol methods established yet. Therefore, quality cannot always be assured, especially not in emergency analytics (10, 7). Obviously, an analysis error had initially occurred in the reported case: the first lab involved was unable to detect ethylene glycol in the patient's serum while the laboratory involved later (a laboratory specialised on bio analysis of glycols and glycol ethers with more than 25 samples per year) measured the highest ethylene glycol levels ever reported in paediatric cases. A third laboratory reconfirmed the analytical results.

In all emergency cases, initial therapeutic decisions are based on preliminary diagnosis without analytic results. Therapy guidelines have been developed by the American Academy of Clinical Toxicology (AACT), Table 2 (11). The most important objective of specific treatment is the termination of production of glycolic acid. Since 1950, ethanol is used as an effective and inexpensive antidote. Considerable adverse effects, i.e. sedation, vomiting, risk for hypoglycemia, and the common problem maintaining the therapeutic plasma concentration (500–1000 mg/L) make ethanol therapy problematic (5,12). Fomepizol (4-methylpyrazol) is an alcohol dehydrogenase inhibitor 8000 times more potent than ethanol. It has a wide therapeutic index. Only minor adverse effects are reported, especially no CNS effects. The AACT recommends fomepizol as the drug of first choice in ethylene glycol intoxications (11,5). Several case reports on treatment of children with fomepizol have been published. Therapeutic success and adverse effects are comparable to adult cases (13,14). Therefore, today fomepizol seems to be the antidote of first choice also for children with ethylene glycol intoxication. Since 2002 fomepizol is registered in the European Union and is available in all member states. Unfortunately, it is only on stock in very few centres. Further important therapeutic procedures

are decreasing acidosis and hypovolemia by intravenous application of sodium bicarbonate and salt solution, respectively. In addition, electrolyte dysbalances have to be corrected (12). In case of severe metabolic acidosis, severe electrolyte dysbalance, or increasing acute renal disorder haemodialysis is recommended.

If fomepizol is used as antidote in ethylene glycol poisoning haemodialysis is only rarely necessary (13). If fomepizol is not available, most but not all leading textbooks on clinical toxicology and the Poisindex database (15) recommend haemodialysis at ethylene glycol serum levels above 500 mg/L. We have been unable to identify any publication that explains the rationale for this recommendation. Furthermore, to our knowledge no published study has shown scientific evidence for superior efficacy of ethanol combined with haemodialysis compared with ethanol alone with respect to frequency of renal insufficiency or other complications or sequelae. One should be aware that metabolites and not unchanged ethylene glycol are responsible for toxicity. It is therefore reasonable, to stop metabolism instead of eliminating the toxic results of metabolism afterwards. In our opinion, the above-mentioned recommendation of haemodialysis did not sufficiently include these considerations. In the case described here the ethylene glycol serum concentration detected was 3900 mg/L. The patient has been treated successfully with ethanol. Therefore, recommendations for haemodialysis in ethylene glycol poisoning should be re-evaluated and possibly exchanged for ethanol therapy only—at least in the paediatric age group.

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Complete unilateral leg duplication with ipsilateral renal agenesis

Christian Lilje (lilje@uke.uni-hamburg.de), Leron J. Finger, Robert J. Ascuitto

Department of Pediatrics, Tulane University Health Sciences Center, New Orleans, USA

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Correspondence

Dr. Med. Christian Lilje,
Kinderkardiologie, Univ.-Herzzentrum Hamburg,
Martinistr. 52, D-20246 Hamburg, Germany.
Tel.: +49 40 42803-3718 |
Fax: +49 40 42803-6826 |
Email: lilje@uke.uni-hamburg.de

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Abstract

A case of a 5-month-old infant with complete duplication of the right leg and ipsilateral renal agenesis is presented. There was also a duplicated scrotum, posterior urethral valves with hydronephrosis, abnormal pelvic bones, and a ventricular septal defect. Complete caudal duplication is exceedingly rare. Associated defects are common. Several aetiological theories have been proposed. Among them, an underlying polytopic (acro-renal) developmental field defect has been suggested. It best explains the specific findings in our patient. However, the aetiology of caudal duplication syndromes may be multifactorial. In the light of twinning theories, associated duplication of hindgut derivatives should be suspected in similar cases. Further research is needed. The motor-skeletal functional outcome after leg duplication surgery is mostly favourable.

Conclusion: A case of complete unilateral leg duplication with ipsilateral renal agenesis is presented. It appears to support the theory of a polytopic developmental field defect.

INTRODUCTION

While partial duplication of the lower extremities is relatively common, complete duplication is exceedingly rare (1,2). The combination of complete unilateral leg duplication with ipsilateral renal agenesis has rarely been observed (1–5). A non-random association has been postulated (2).

CASE REPORT

A 5-month-old boy with complete duplication of the right leg was transferred for moderately severe congestive heart failure due to a ventricular septal defect (VSD). The pregnancy had been uneventful with no history of maternal drug or toxic substances abuse. The family history was negative for congenital malformations or consanguinity.

On physical examination, there was an accessory anterior limb with a rudimentary foot (Fig. 1). The main right leg showed poly- and syndactyly. Other findings included an accessory left-sided nipple, and a duplicated scrotum. There was a grade 3/6 systolic ejection murmur at the left mid-sternal border. Radiographic studies (e.g. Fig. 2) further defined the osseous malformations with elements of the VACTERL association. The tibia of the accessory right leg was shortened and malformed. The femur was fully formed, but there was only a rudimentary articulation with the deformed pelvis. An additional iliac wing-like structure, an auxiliary ischial bone, and an extra pseudo-acetabulum were found. Both main lower extremities appeared unremarkable and symmetric except for the right-sided forefoot abnormalities. The leg perfusion was non-compromised by Doppler ultrasound studies. A hemi-vertebra was present at the level of the 10th and 11th thoracic vertebrae. Abnormal pelvic bones partially impinged on the rectum. The right-sided kidney and adrenal were absent (Fig. 2). A right pelvic or multicystic dysplastic kidney was excluded by computed tomography. There was posterior urethral valves and vesico-ureteral re-

flux. Transthoracic echocardiography displayed a large VSD. Notably, there was no urinary or intestinal tract duplication and no omphalocele.

At four months of age a vesicostomy had been performed for hydronephrosis. The scrotal duplication was resected. The VSD was closed surgically upon arrival at our institution. At 6 months of age, a tracheostomy was performed for chronic respiratory failure. Simultaneously, a Nissen fundoplication was done with placement of a gastrostomy button for gastro-esophageal reflux. The bony rectal compression eventually necessitated a sigmoid colostomy. The patient is awaiting resection of the accessory anterior limb. The motor-skeletal functional outcome after surgery is mostly favorable (1).

DISCUSSION

Leg duplication is frequently associated with additional anomalies. A non-random association is mostly agreed upon. Several aetiological theories have been proposed and continue to be debated.

Incomplete caudal twinning (6,7). By duplication or splitting two organizing centres form within a single embryonic disc. Sagittal symmetric pairing of axial embryonic structures occurs. Legs, pelvic structures and hindgut derivatives may be duplicated (7,8). The hindgut develops from the caudal cell mass, which appears to be particularly vulnerable. A refined version is the concept of a *disruptive sequence* (8). The caudal cell mass may be crossed and divided by fibrous remnants of Kovalevsky's canal, an epithelial structure transiently interconnecting amniotic and yolk sacs.

Error of limb bud specification (9–11). Limb duplication may occur by splitting of the limb bud or by induction of supernumerary limb buds. Axial limb specification is influenced by a group of specialized mesodermal cells that reside



Figure 1 Clinical appearance at 8 months of age. The accessory right leg is located anteriorly (arrow). There is poly- and syndactyly of the primary right foot. Tracheostomy and sigmoid colostomy had been performed.



Figure 2 Axial CT scan of the abdomen (top), pelvis (middle) and lower extremities (bottom). The right-sided kidney and adrenal are absent. At the level of the left-sided kidney (*lk*) the corresponding space on the right between liver and psoas muscle is empty (arrow). While the accessory right femur is fully formed there is only a rudimentary pelvic articulation. *Ar*l, accessory right leg; *ll*, left leg; *mr*l, main right leg; *sp*, spine.

at the caudal border of the limb bud. They produce a diffusible morphogen. Should its local concentration be high in more than one region more than one limb bud will occur.

Polytopic (acro-renal) developmental field defect (1–3,12). At the end of the 4th week of gestation, the lower limb buds and the mesonephric buds are in close proximity functioning as a developmental field. Different teratogens result in the same pattern of anomalies (1,8). It has been speculated that insulin like growth factors (IGF) are responsible for a mesonephric cell error which leads to accessory limb rather than renal specification (2,13). IGF such as IGF-I are produced by the mesonephros and are present in the nearby limb buds in animal models (2).

Genetics (1,7). Genetic mechanisms may also play a role. The mouse model *disorganization*, a semi-dominant gene with incomplete penetrance, is known to cause a variable spectrum of anomalies, among them limb duplication with renal agenesis (14). A possible human homologue has been presented (15).

All of the above theories provide valid arguments for leg duplication processes. Incomplete twinning and disruptive sequences would also explain the associated polydactyly and scrotal duplication. However, in our patient further elements of the stereotypical hindgut duplication pattern (8) were not found. The renal agenesis is not explained by these theories either and not by error of specification concepts. The latter, however, allow to estimate the basic teratogenic insult at approximately the fourth week of gestation (11). The best explanation for the unilateral leg duplication – ipsilateral renal agenesis association is provided by and thus supports

the theory of a polytopic developmental field defect. Genetic mechanisms may be involved.

The specifics of findings in our patient are unusual. The aetiology may be multifactorial. Further research is needed. In case of leg duplication, additional defects should be searched for.

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Haemolysis alters plasma flecainide levels in newborn infants

M Vento (maximo.vento@uv.es, maximovento@telefonica.net)¹, B Fernández Tudela¹, R Escrig², P Sáenz¹, A Sánchez³, A Cano³

1.Division of Neonatology, Hospital Materno-Infantil La Fe, Valencia, Spain

2.Fundación Hospital La Fe, Valencia, Spain

3.Division of Cardiology, Hospital Materno-Infantil La Fe, Valencia, Spain

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Correspondence

Maximo Vento, PhD, MD, Servicio de Neonatología, Hospital Universitario Materno-Infantil La Fe, Avenida de Campanar, 21, E-46009 Valencia, Spain.

Tel.: +34 96 386 2791 | Fax: +34 96 197 3408 |

Email: maximo.vento@uv.es,

maximovento@telefonica.net

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Abstract

Refractory neonatal supra-ventricular tachycardia may require the use of flecainide as anti-arrhythmic. Close control of plasma levels is mandatory due to pro-arrhythmic complications. However, inadvertent hemolysis during blood sampling may cause an increase in measured plasma flecainide concentrations. We conclude, therefore, that dosing of the drug should be always done with caution, and in case of suspected haemolysis plasma levels should be repeated with a new blood sample.

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INTRODUCTION

The most commonly presenting pathological tachycardia in the newborn is a narrow complex supra-ventricular tachycardia (SVT) (1). In an infant without obvious circulatory compromise, identification of the tachycardia and its management with either facial immersion in cold water or rapid injection of intravenous adenosine is uncontroversial (2,3). However, management of the infant with circulatory com-

promise, or with a history of foetal hydrops, antenatal polypharmacy, prematurity or congenital heart disease is more difficult. There is a risk of death from the underlying problem or due to inappropriate or inadequate treatment, and an understanding of the mechanisms of tachycardia is important to make a logical management plan (4). Choice of anti-arrhythmic drugs is based on the severity of the presentation,

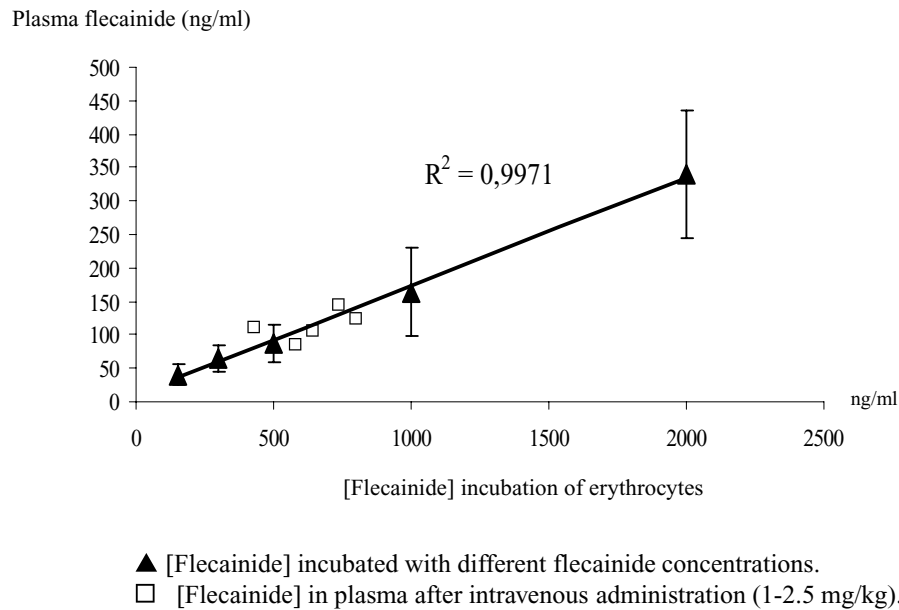


Figure 1 Plasma flecainide incubated with different flecainide concentrations.

the mechanism of the tachycardia, and other factors such as proximity to a hospital and a doctor's personal experience (3,4). For a well tolerated, adenosine sensitive tachycardia, the choice would be a long acting β -blocker. However, in unresponsive infants, a more powerful anti-arrhythmic drug, such as sotalol, flecainide or amiodarone, may be required (5). Notwithstanding, flecainide may cause serious QRS widening and even death secondary to ventricular fibrillation (5–10). In order to avoid these complications, strict control of plasma levels (safety range 0.2–1 mcg/mL) have been recommended to ensure that toxic concentrations are not reached (8–10).

We have experienced in clinical practice that haemolysis during blood sampling causes variations of plasmatic levels of flecainide. Since flecainide is a polar substance, which easily diffuses into the erythrocyte's cytoplasm, plasma levels may only partially reflect total amount of drug present in whole blood. Therefore, haemolysis may cause measured plasma levels to differ from those in vivo giving rise to dosage alteration based on erroneous data.

We hypothesize that knowing the increase in flecainide plasma levels caused by complete haemolysis, would allow to set up the limits of security in the dosage of this drug.

In order to verify our hypothesis, we incubated blood aliquots of newborn infants with SVT before initiating treatment with different concentrations of flecainide, and determined its concentration before and after inducing haemolysis, and calculated the percentage of variation of the drug levels before and after haemolysis.

MATERIAL AND METHODS

Five millilitres of whole blood was drawn with a heparinised syringe from five newborn infants with SVT before initiating

flecainide administration. Haematological determinations (red blood cell count, haemoglobin concentration, haematocrit) were first determined. Five aliquots of 0.6 mL of each infant were incubated with flecainide acetate at concentrations equivalent to 150, 300, 500, 1000 and 2000 ng/mL. After 1-h incubation and vortexed for 20 s, blood samples were split in two of 0.3 mL. One of the aliquots was centrifuged at low-speed ($900 \times g$ for 5 min). Plasma was deproteinised by addition of two volumes of acetonitril, vortexed for 20 sec and then centrifuged at $10\,000 \times g$ at 4°C for 10 min. Forty microlitres of the clean upper layer were injected directly onto the chromatographic system. The second aliquot was similarly processed and plasma obtained. In addition, the red cell mass was washed twice with NaCl 0.9%. The supernatant was aspirated and the cell pellet weighed and haemolysed with 0.1 mL of distilled water. The resulting solution was added to plasma and injected directly onto the chromatographic system.

Determination of plasma flecainide levels by liquid chromatography and mass spectrometry (LC-MS/MS)

LC-MS/MS was carried out using a Quattro Micro triple-quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with a Shimadzu LC-10ADvp pump, and a SLC-10Avp controller system with a SIL-10ADvp autoinjector. Samples were analysed by reverse-phase high performance liquid chromatography using a Teknokroma (Barcelona, Spain) Tracer Excel 120 ODSB column (5×0.21 cm) with $5 \mu\text{m}$ particle size. In all cases $40 \mu\text{L}$ were injected onto the column. The following gradient system, pumped through the column at 0.3 mL/min , was used (min/%A /%B) (A, 0.1% formic acid; B, methanol): 0/95/5, 5/95/5, 10/5/95, 15/5/95, 15.1/95/5 and 20/95/5. Positive

Table 1 Comparison between flecainide concentrations expressed in nanogram per gram of haemoglobin (ng/g Hgb) in plasma and haemolysed blood of term newborn infants incubated with flecainide acetate at five different concentrations of the drug

Flecainide concentration at incubation ng/mL	Plasma flecainide concentration (ng/mL) (n = 5)	Plasma flecainide (ng/g Hgb) (n = 5)	Haemolysed blood flecainide concentration (ng/g Hgb) (n = 5)	Significance Plasma flecainide versus haemolysed blood flecainide (ng/g Hgb)
150	43.5 (12.9)	3.04 (0.9)	3.94 (0.98)	0.001
300	64.5 (19.5)	4.53 (1.4)	5.50 (1.32)	0.002
500	86.1 (20.0)	6.05 (1.4)	7.27 (1.57)	0.008
1000	162.4 (54.0)	11.43 (3.8)	13.16 (3.2)	0.001
2000	338.8 (95.6)	23.85 (6.7)	28.52 (7.7)	0.004

n: number of patients.

Values of the five determinations per patient are expressed as mean with standard deviation in parentheses.

ion electro-spray tandem mass spectra were recorded with capillary voltage 5000 V, cone voltage 30 V, desolvation gas 400 L/h, cone gas 30 L/h, source temperature 120°C, desolvation temperature 500°C, collision energy 25 eV. An assay based on LC-MS/MS with multiple reaction monitoring was developed using the transitions m/z 416.5–399.3.

Calibration curve of plasma flecainide

Calibration curve for flecainide was obtained using a standard of flecainide in plasma at five different concentrations ranging from 150 to 2000 ng/mL. Flecainide was incubated in plasma for one hour and processed as described before. Five determinations were performed at each different concentration, and the mean plotted in the calibration curve, which was linear and with a correlation coefficient >0.99 . Patients' plasma flecainide concentration after intravenous administration shown adjusted to the calibration curve (see Fig. 1).

Comparisons between the different flecainide values have been done using non-parametric statistics with a α degree of significance of 5%.

Parent's informed consent and Ethical Committee approval were obtained.

RESULTS

Blood haematocrit median was of 50.4% (P50%: 46–P95%: 57) and haemoglobin (Hgb) 14.8 (P50%: 12.6–P95% 16.4) g/dL.

Plasma flecainide concentrations (mean $\pm$ standard deviation) expressed in ng/mL are shown in Table 1. Flecainide plasma concentrations at incubation (before and after haemolysis) have been expressed as ng/g Hgb (see Table 1) because Hgb concentration remained constant before and after haemolysis. Table 1 also shows that flecainide levels in totally haemolysed samples were significantly higher in each different incubation point as compared to concentration in non-haemolysed samples (23.0% at 150 ng/mL; 21.4% at 300 ng/mL; 20.1% at 500 ng/mL; 15.1% at 1000 ng/mL and 19.5% at 2000 ng/mL).

DISCUSSION

SVT in infants can be refractory to single-drug therapy (3). Although, one may consider interventional therapy, this option may carry a high risk of morbidity and mortality. Moreover, tachyarrhythmias in infants often have a favourable resolution thus reinforcing the importance of selecting an effective medical regimen (3–5). Flecainide alone or together with amiodarone or sotalol has been shown to be effective in controlling refractory tachyarrhythmias (5). However, flecainide may cause serious side effects such as QRS widening, life-threatening ventricular fibrillation, or even death (6–10). Thus, very strict control of plasma levels of the drug is mandatory. However, we have frequently experienced that a certain degree of inadvertent haemolysis may be associated with blood sampling under difficult clinical conditions. In this situation, plasma levels of flecainide are substantially increased. Our model shows that a certain proportion of flecainide accumulates within the erythrocytes, and thus not made evident in the routine plasma level determinations. At higher incubation concentrations of flecainide, differences between haemolysed and non-haemolysed samples become smaller, which may be due to saturation of erythrocytes with the drug. Moreover, in relation to the degree of haemolysis during blood sampling in the clinical practice, no previous reports have been published.

To conclude, it is important to note that the use of flecainide requires strict control of plasma levels of the drug within a safety range. In case of suspected haemolysis or unexpected variation of the plasma drug level, this should be immediately repeated using a new blood sample.

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Temporary henna tattoo is unsafe in atopic children

Stefania Corrente (stefy3@tiscali.it), Viviana Moschese, Marco Chianca, Simona Graziani, Roberta Iannini, Maria La Rocca, Loredana Chini

Pediatric Allergology and Immunology Center, Azienda Ospedaliera Universitaria Policlinico Tor Vergata, University of Rome Tor Vergata, Italy

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Correspondence

Stefania Corrente, University of Rome Tor Vergata, Pediatric Allergology and Immunology Center Viale Oxford, Rome 00133, Italy.
Email: stefy3@tiscali.it

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Abstract

Temporary henna tattoos have become increasingly popular as a safe alternative to permanent tattoos among American and European children and teenagers during the summer holidays.

Currently, temporary henna tattoos contain not only henna, but also other additives such as para-phenylenediamine (PPD), which is considered to be the chemical agent that most frequently causes skin reactions associated with the use of commercial black henna.

In this report, we describe an 11-year-old boy who applied a temporary black henna tattoo on his right arm during the summer holidays in Greece and developed a severe contact dermatitis at the tattoo site with residual hypopigmentation.

He had no previous history of contact dermatitis, however he did suffer from seasonal allergic rhinitis and atopic dermatitis.

Patch testing revealed a strong reaction to PPD, a substance commonly contained in temporary henna tattoo preparations.

Conclusion: Henna tattoos are an increasing problem worldwide since they carry an increased risk of severe skin reactions; therefore we suggest that the use of temporary henna tattoos in children be discouraged.

INTRODUCTION

Streetside temporary henna tattoos have become increasingly widespread among American and European children and teenagers; this practice is popular during holidays for the rapidity of execution and the presence of seasonal artists, especially on the beaches along the Mediterranean Sea and elsewhere.

The most common dye for such temporary tattoos is henna, a greenish powder made from the dried leaves and flowers of *Lawsonia alba* or *inermis*, a shrub cultivated in North Africa, India and Sri Lanka. Lawsone, a naphthoquinone, is the active dye and is considered the main allergen in henna.

Henna is used worldwide as a hair dye, as a component of some shampoos and cosmetic products and also in traditional Islamic communities during marriage ceremonies and other celebrations to draw floral or geometric motifs on the hands and feet of participants; the tincture is also used as an antimycotic treatment.

Several types of henna are available and are characterized by the shade they give to hair: neutral, red, brown or black. Egyptian henna is the green henna powder that imparts a red-brown colour to hair. All the other colours obtained from henna are actually due to the addition of other dyeing agents to natural henna (1).

Henna leaves are ground into a powder and mixed with water to create a paste which is applied to the skin and left to dry from 5 min to 24 h. The longer henna is put in contact with the skin, the darker the resulting colour will be.

For this reason to enhance its colouring effect and to shorten the time of application henna is often used in combination with additives such as instant coffee powder, beet juice or 'secret formula' containing varying amounts of lemon oil, vinegar, eucalyptus oil, clove oil and para-phenylenediamine (PPD).

PPD is a substance familiar to the cosmetic industry and is used in oxidising hair dyes; it is a strong skin sensitizer

and can cause contact dermatitis (2–6) or, less commonly, immediate type hypersensitivity reaction with angioneurotic oedema and collapse (7).

We describe the case of an atopic young boy who presented a contact dermatitis to a paint-on 'tattoo' with residual hypopigmentation at the site of the eczematous lesion.

CASE REPORT

An 11-year-old boy, with a history of atopic dermatitis and rhinitis to several allergens (Grasses, Dermatophagoides and Olive tree) had a temporary black henna tattoo on his right arm during his summer holiday in Greece. The 'artist' painted the skin by directly applying a paste from a tube of henna preparation; the tattoo was then left to dry.

Seven days later, he developed an itchy and oedematous eruption at the site of the henna tattoo. He was first treated at home with topical hydrocortisone for 20 days with no improvement.

At the time that he came for a consultation to our Pediatric Allergology and Immunology Outpatients Clinic at Policlinico Tor Vergata an eczematous reaction on his right arm was observed: the skin was erythematous, oedematous, papulovesicular and infiltrate. Topical pimecrolimus 1% and oral desloratadine 5 mg/day were prescribed with gradual clinical improvement.

Post inflammatory hypopigmentation at the tattoo site was still present 6 months later.

The boy had no history of skin reaction of this type and denied any prior contact with hair or skin dyes.

His sister, with no history of allergy, had a similar 'tattoo' from the same artist with no reaction.

Two months later, patch testing (Alk-Abellò) to the European standard series containing hair dyes and textile dyes was performed on the upper back of the patient, using the Finn Chamber technique. At 72 h, a very strong (+++++) reaction to PPD characterized by intense erythema, infiltration and vesicles and a weak (+) reaction to Kathon was observed.

Prick testing (Stallergenes) to various allergens including Latex was performed with confirmation of a previous sensitization, but with no sensitization to Latex as expected, since he had not undergone an application of a tacky transfer prior to the black henna (Table 1).

DISCUSSION

Contact dermatitis or immediate-type hypersensitivity reaction with urticaria, sneezing and respiratory symptoms to natural henna are rarely reported (8–9), while commercial black henna containing PPD is associated with skin reaction after temporary tattooing, both in adults and children (2–6).

While henna body paintings have been used in certain cultures for many centuries, the use of henna paste for temporary tattoos has become very popular in western culture in recent years as a safe alternative to permanent tattoos.

As henna tattoo is a lengthy and tedious procedure, many additives such as PPD may be added to the mixture to accel-

Table 1 Prick test results

Allergen	Reaction
Grasses	++++ [†]
Herbaceae	++++
Dermatophagoides	+++
Cat	+++
Dog	++
Poplar	+
Olea	+++
Alternaria	Neg
Latex	Neg

[†]Any weal ≥ 3 mm in diameter compared to the negative control test weal (allergen diluent) was considered positive (+).

erate the process, to darken and give more precision to the design (10).

As in the other cases described (2–6), our young patient had an eczematous reaction to a henna tattoo. Although the chemical compounds contained in the preparation were unknown, the strong reaction that our patient showed to PPD on patch testing makes us believe that PPD was the main allergen responsible for the cutaneous reaction following henna tattooing. Interestingly, the patient had never experienced contact dermatitis or sensitization to hair or skin dyes throughout his life. Hence, the duration of contact might represent a significant factor since in our patient active sensitization did occur at the first exposure but very likely developed because of prolonged direct skin contact.

PPD is a powerful skin sensitizer and it is often present in henna at high concentrations (15.7%) (10), in spite of the directive of the European Community which allows a maximum concentration of 6% for PPD and other diamino-benzene as hair dye only (11).

The application of PPD to skin is also prohibited in USA according to FDA (12).

Moreover, the sensitizing properties of PPD might be increased by other factors like the presence of various oils, solvents and ultraviolet light and/or the lack of an oxidizing agent in the mixture.

Last but not least, due to PPD cross-reacts with a number of structurally related compounds that have an amino group in para position of their benzene ring, i.e. azo dye, sulphonamide, p-amino benzoic acid sunscreen and local anaesthetics such as benzocaine and procaine, PPD sensitization can cause either direct or indirect allergic reactions substantially affecting the quality of life and working potentials (13).

Furthermore, traditional henna belongs to Lythraceae family, thus strong prick test reaction to Herbaceae mixtures, as in our patient, might be an additional drawback to using henna as a tincture.

In conclusion, since temporary henna tattoos do not undergo rigorous control of materials and sources by local governments, they can be associated with severe

cutaneous complications and therefore their use should be limited.

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