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CASE REPORT

PATHOLOGY/BIOLOGY

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Death Following Injection Sclerotherapy Due to Phenol Toxicity*

ABSTRACT: Prolapse rectum (PR) or protrusion of the rectum beyond the anus occurs frequently in populations at both extremes of age. In the pediatric population, in developed countries, the commonest cause for PR is thought to be cystic fibrosis (CF). Treatment options for CF include conservative management, surgical resection and fixation, suturing, and injection sclerotherapy (IS). The last is considered an attractive treatment option because it is minimally invasive. In this case report, the authors present the details about a 2-year-old female child, with PR and CF, who died after IS, using phenol as the sclerotherapeutic agent. Autopsy findings and toxicology tests performed to establish phenol toxicity are documented. The available literature is reviewed. This case report underscores the risks of using phenol for IS and emphasizes the point that the procedure is not innocuous and an adverse outcome including fatality is a possibility.

KEYWORDS: forensic science, pathology, sudden death, injection sclerotherapy, phenol toxicity, prolapse rectum, cystic fibrosis, autopsy

Prolapse of the rectum (PR), or protrusion of the rectum beyond the anus, has been described as early as 1500 BC (1). PR is divided into two distinct types: full thickness prolapse, defined as protrusion of the entire thickness of the rectal wall through the anus; and mucosal prolapse where only the rectal mucosa protrudes from the anus. PR occurs frequently in populations at both extremes of age. It frequently presents as a self-limiting disorder in children younger than 4 years of age (2). In adults, the peak incidence of PR is after the fifth decade of life. The conditions leading to PR as summarized in Table 1 show a distinct dichotomy in its etiology. The causative factors for PR in developing countries is usually related to gastroenteritis, parasitic infestations, and malnutrition (3). In the developed world, a common cause for PR is cystic fibrosis (CF), presumably related to malnutrition, poor muscle tone, and passage of large bulky or voluminous stools (2). It is estimated that *c.* 20% of patients with CF probably will experience PR at some time (2). However, CF is not the most common cause of PR in childhood (4). In a recent study of pediatric patients with mucosal prolapse, 28% had chronic constipation, 20% had acute diarrhea, 11% had CF, 24% had a variety of neuromotor problems, and 16% no identifiable cause (5). The entire topic of PR, including its rich and entertaining history, has been well reviewed recently (6).

The therapeutic options for PR are summarized in Table 2. Most cases respond to conservative treatment within 1 year (2). However, in some children, the condition persists, requiring surgical intervention. Surgeons have shown considerable ingenuity in the search for the ideal therapeutic option for PR. Over 200 different techniques have been employed, including abdominal or perineal and laparoscopic approaches to resect/repair and fix the levator ani muscle, presacral packing with mesh, the use of Thiersch's wire, and other suture materials (2). The surgical options for treatment/management of PR have been well reviewed by Poritz (1), Karluf et al. (6), and Madiba et al. (7).

Injection sclerotherapy (IS) is a popular treatment option as it is minimally invasive. IS induces intense fibrosis between the rectal mucosa and submucosal tissue, and subsequent fixation of the rectal mucosa to the underlying rectal wall (3). In the past, a variety of compounds including ergot, alcohol, glycerin, strychnine, and white oak bark, etc., have been used (8). L. Findlay, while a resident in Geneva in 1919, first observed the procedure being performed by Prof. E. D'Espine and recommended the use of alcohol (9). In recent times, IS is most frequently performed using saline or phenol as the sclerosant (3). We report a case of sudden death in a 2-year-old girl with CF and PR who died after IS with phenol. With this report, we are underscoring the risk of phenol-based IS.

Case Report

A 2-year-old female child, with refractory PR, CF, and mild Ebstein malformation of the tricuspid valve was brought to the operating room for IS, using a 5% phenol in almond oil solution. In the operating room, after induction of general anesthesia, the child received a 5-point injection in the submucosal plane around the rectum. Ten milliliters of the solution was injected, with *c.* 2 mL at each point. According to the surgeon, the procedure was performed under direct visual observation. Confirmation of appropriate placement of the syringe at each point of injection was made by aspirating the syringe, without return of blood. Within 5 min of

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TABLE 1—*Conditions associated/predisposing to development of prolapse rectum.*

A. Increased bowel motility
1. Organisms causing diarrhea
a. Parasitic
Amebiasis
Giardiasis
Trichuriasis
b. Bacterial
Salmonella
Shigella
E. coli 0157:H7
2. Noninfectious causes
Ulcerative colitis
Laxative abuse
B. Increased abdominal pressure
Chronic constipation
Protracted coughing
Excessive vomiting
Straining at urination (phimosis)
C. Congenital conditions
Cystic fibrosis
Myelomeningocele
Hirshsprung's disease
Spina bifida
Congenital hypothyroidism
D. Miscellaneous conditions
Mucosal polyps/ tumors
Imperforate anus, status postrepair
Malnutrition, unspecified

TABLE 2—*Medical and surgical treatment options for PR in children.*

Medical	Surgical
Manual replacement	Anal encirclement
Support for perineum	Excision and resection
Defecate while recumbent	Injection sclerotherapy
Tape buttocks	Packing
Paregoric therapy for diarrhea	Linear cauterization
Stool softeners for constipation	Rectopexy

the conclusion of the injections, the baby experienced a sudden cardiac arrest and received cardiopulmonary resuscitation for *c.* 2 h. She developed anoxic encephalopathy, rhabdomyolysis with elevated total creatine kinase (CK) levels of 1034 U/L (reference range 30–135), and disseminated intravascular coagulopathy (DIC). The CK levels were not fractionated. No specimen was submitted for toxicology at the time of testing for CK. She died *c.* 4 days after the surgery. A urine specimen submitted 23 h after the surgery had a total phenol concentration of 240 mg/L (reporting limit 1.0 mg/L).

At autopsy, the child's external appearance and internal organs were appropriate for age. There was an intense red discoloration around the anus, spreading to a wider area of brown discoloration involving the buttocks. Internally, there were multiple punctuate hemorrhages, consistent with DIC, on the mesentery and capsule of thoracoabdominal organs. There was intraparenchymal hemorrhage within the lungs and spleen, and red blood cell casts within the renal pelvis. The anal canal was infracted on histological examination. The rectum was grossly normal. The evaluation of the heart (48.2 g) confirmed the mild low implantation of the tricuspid valve consistent with Ebstein malformation. The psoas muscle biopsy, with myophosphorylase, cytochrome oxidase, succinate dehydrogenase, and adenosine triphosphatase enzyme studies, revealed nonspecific myopathic changes with decreased myophosphorylase and glycogen. These tests for enzyme activity in the muscle fibers were used to rule out a congenital disorder of muscle metabolism. The section of liver showed mixed Periodic acid Schiff (PAS) stain positive and both Peri-iodic Acid Schiff with Diastase (PASD) stain positive and PASD negative micro- and macrovesicles in the hepatocytes. The microvesicles were PAS and PASD positive and were identified as microvesicles containing glycogen. The macrovesicles were PAS positive, PASD negative, and consistent with steatosis. The findings together indicate acute liver injury. Examination of the brain revealed cerebral edema with acute hemorrhagic infarct of the left occipital cortex, and multifocal subarachnoid, cortical, and cerebellar hemorrhages. There were fibrin thrombi in all tissues. There were no significant gross or microscopic changes of CF in the lungs or pancreas.

Discussion

IS has been deemed a very attractive and minimally invasive option for the management of PR. A variety of compounds have been tried in the past with variable success (8). The current methods reported in the literature involve the use of alcohol, saline, and phenol as the sclerosant (3). Our case report highlights the narrow therapeutic index of phenol and the calamitous adverse effect it can produce. While this is not the first report describing the severe toxicity after exposure to phenl, this the first report regarding a fatality after phenl use for IS.

Phenol (carbolic acid: molecular formula C_6H_6O) is the simplest member of a group of aromatic compounds. It is a colorless crystalline solid with a sweet tarry odor. It has strong antiseptic properties and was used by Sir Joseph Lister in his pioneering innovations in antisepsis during surgical procedures (10). Phenol is a protoplasmic poison, which disrupts cell wall and denatures proteins, and a strong acid, which causes caustic injury on topical application. Because of its toxicity, it is rarely used as an antiseptic today. Of special interest to the forensic community is the data that in 1909, of the 3376 poisoning-related deaths that was reported in the United States, 1621 (48%) were because of phenol of which 1466 (90%) were suicide (10).

Phenol is used commercially as a disinfectant, industrially as an intermediate in chemical synthesis, and medically as an ingredient in Anbesol, Campho-phenique, and Chloraseptic, as well as to produce sympathetic nerve block in patients with chronic peripheral vascular disease (11). Exposure to phenol, in the industrial context, may occur by inhalation of the vapor, by cutaneous absorption, or by oral ingestion (12,13). In the medical context, exposure to phenol occurs when it is used for IS or in dermatology as a chemical peel.

Phenol causes severe irritation and corrosion on skin contact or other tissues. It is a caustic and causes injury by coagulative necrosis. Systemic absorption has been documented to produce cyanosis, shock, weakness, cardiac arrhythmia, collapse and convulsion, liver and kidney failure, coma, and death (11). Phenol has excellent dermal penetration and topical exposure has resulted in severe burns as well as severe systemic toxicity (14,15). Phenol preparations have been used in dermatology and plastic surgery for the treatment of acne and during chemical face peels. During cutaneous application of phenol, absorption of the chemical has occurred with deleterious systemic effects, including cardiac arrhythmias (16). The mechanism of death in this case presented was complications of cardiac dysrhythmia. The rhabdomyolysis was secondary to the anoxic brain injury. The ancillary tests were used to rule out congenital causes of cardiac dysfunction.

TABLE 3—*Summary of survivors and fatalities because of phenol exposure as published in the literature.*

Author and Reference	Age	Predisposing Condition	Compound Exposed To	% of Phenol	Route of Absorption	Phenol Concentration Blood (mg/dL)	Phenol Concentration in Urine (mg/dL)	Tissue Type	Tissue Concentration (mg/100 mg)	Outcome	Comments
Soares and Tift (10) Case 1	43 years old	Mental illness	Castellani's paint	Unknown	Unknown	5.6		Liver	7.4	Death	Found dead; blood alcohol 0.03 gm%
Soares and Tift (10) Case 2	4 weeks old	Seborrheic dermatitis	Castellani's paint to body	Undiluted	Dermal					Death	Collapsed 5 h after application, died 7 h later
Soares and Tift (10) Case 3	17 years old	Chemical splash 15% of BSA exposed	Chemical splash on body	30	Dermal	2.7				Death	Found dead; blood alcohol 0.03 gm%
Bentur et al. (14)	47 years old	Driver of chemical laden truck 3% of BSA exposed	Chemical spill on foot	90	Dermal	Serum 21.6				Survived	Prolonged elimination half-life
Unlu et al. (16)	11 years old	Xeroderma pigmentosum 15% of BSA exposed	Chemical peel to body	88	Dermal	58.9				Survived	Aggressive therapy
Gupta et al. (19)	50 years old	Chronic back pain	Injection of phenol solution nerve block	89	Intradermal	8.7				Survived	Hemodialysis
Lewin and Cleary (15)	24 years old	Benzylbenzoate application for scabies brush dipped in phenol	Phenol used as aniseptic	80	Dermal	0.47	Nil	Liver (hydrolyzed)	0.00071	Death	Collapsed minutes after application, died soon after
Horch et al. (21)	22 years old	Splash from pipeline 20.5% of BSA exposed	Phenol solution	Unknown	Dermal	1.74	56.6			Survived	Hydration and diuresis
Cronin and Brauer (20)	10 years old	Aggressive Rx for cutaneous burns with foille	Phenol and carbisulphoil	*c.* 2	Dermal	22				Death	Died 4 days postprocedure
Dico et al. (22)	40 years old	Mental illness	Phenol solution		Oral	13	4.7	Brain	0.0486	Death	Found dead
Tanaka et al. (23)	27 years old	Presumed ingested from wrong container while intoxicated	Phenol/ chloroform mix		Oral/dermal	6	20.8		87.4	Death	Found dead
Philip and Marraffa	2 years old	Injection sclerotherapy	Phenol in almond oil	5%	Injection		24			Death	Cystic fibrosis and Ebstein anomaly Died 4 days postoperative

The units of measurement in some of the articles had to be converted for standardization of data.
BSA, body surface area.

A variety of sclerosing agents have been used with varying success rates. The publications about the value of the use of phenol as sclerosing agent for PR have been mixed. One report indicated 89% cure rates after one or two injections (17). This study reported 100% cure rates after three injections and documented no complications. Another study reported 91 of 100 (91%) cure rate after one injection and 100% cure rate after two injections and no complications (18). Another report indicated complications, including mucosal sloughing and perianal fistulae, in 27% of cases (3). To our knowledge, this case report is the only report of fatality because of phenol toxicity after IS that has been reported in the literature.

Fatalities following phenol poisoning, because of industrial exposure, from chemical peel, and when used as a local anesthetic have been reported in the literature (10,14,19). The information on the available cases of phenol-related intoxication or fatality is summarized in Table 3. Owing to variation in technology for the testing, etc., a select few cases are discussed later in relation to our case. Soares and Tift (10) document the autopsy findings in three cases, one case of medication overdose, and two cases due incorrect formulation of Castellani's paint. Castellani's paint is a mixture of phenol, basic fuchsin, resorcinol, ethanol, acetone, and water. The concentration of phenol is available in blood in two cases (2.7 mg/dL and 5.6 mg/dL) and in liver of one case (7.4 mg/100 mg wet tissue). Bentur et al. (14) describe a case of industrial exposure when 90% phenol spilled over a man's left foot. He collapsed after 4½ h of exposure. His peak serum phenol concentration was 21.6 μg/mL, and peak urine phenol was 13,416 mg/g creatinine. Gupta et al. (19) describe a case of intoxication after wrong formulation of phenol preparation for nerve block injection (89% instead of the prescribed 6% solution). No phenol concentration in blood is documented on this case.

The only case comparable to our case is reported by Unlu et al. (16). The case involves that of an 11-year-old boy who underwent chemical peel for Xeroderma pigmentosum. He was treated with an 88% phenol solution to about 15% of body surface area in an "apply and rinse" procedure. He developed cardiac arrhythmia and was aggressively treated, and he survived. His urinary phenol concentration of postprocedure day 1 was 58.9 mg/dL but decreased to 19.5 mg/dL on follow-up measurements. Aggressive hydration and hemodialysis therapies were rapidly instituted, and the patient survived. Our case demonstrates the acute onset of cardiovascular collapse secondary to phenol. In our case, however, the patient was aggressively resuscitated for nearly 2 h with successful return of spontaneous circulation at that point. However, because of the prolonged cardiac arrest and hypoxia, she developed expected sequelae of a prolonged down time, including anoxic encephalopathy, DIC, and rhabdomyolysis. Interestingly DIC was not documented in all the reports reviewed by us.

There are three ways to postulate the unfortunate outcome in our case and all involve avenues that will deliver a high concentration of phenol to the systemic circulation. First, a greater amount of drug could have been placed into the solution used. The product was extemporaneously prepared by the hospital pharmacist, and human error could have occurred. We ruled this possibility out by a secondary external analysis of the product used, which confirmed the 3.1% phenol concentration. The original syringe and container was submitted for the phenol concentration testing. Second, the drug was inadvertently delivered directly into the vascular system. However, the surgeons ruled this out as they confirmed that prior to drug administration, there was no blood return to the syringe. The third possibility that a high concentration of drug was delivered into the central compartment because of the same mechanism that has been described previously with dermal application except that in this area of the body (rectal mucosa and associated vascular intimacy/ surface area) in this particular patient, an amount of phenol was absorbed sufficient to produce death. After this tragic incident, one must question the utility of phenol in this procedure when there are other, safer alternatives.

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