

# An unusual mimicker of a sepsis outbreak: ergot intoxication

Ahmet Yagmur Bas · Nihal Demirel · Ahmet Soysal ·  
Kahraman Arslan · Ugur Dilmen

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**Abstract** Methylergonovine (MEV) is a semi-synthetic ergot alkaloid used in the prevention and control of postpartum hemorrhage. This report describes 12 newborns born on the same day in a local country hospital in Turkey and developed sepsis-like symptoms and encephalopathy within the first 6 h of life due to accidental administration of MEV instead of vitamin K in the delivery room. The major features of MEV poisoning were lethargy (41.7%), seizure (75.0%), feeding intolerance (66.6%), hypoventilation (58.3%), irritability (25%), and peripheral circulatory abnormalities (58.3%). As a conclusion, clinical findings of

ergot toxicity in newborns cannot be distinguished from infectious disease or neonatal encephalopathy.

**Keywords** Methylergonovine · Ergot intoxication · Medication error · Sepsis · Newborn

## Introduction

Methylergonovine (MEV) is a semi-synthetic derivative of the amine-alkaloid group of ergot compounds. The structural similarity between ergot alkaloids and the endogenous amines dopamine, norepinephrine, and serotonin accounts for their pharmacologic activity [1, 6]. MEV directly stimulates alpha-adrenergic receptors, resulting to multi-organ ischemia [10]. The features of MEV toxicity are caused predominantly by alteration in vascular tone, affecting circulation to many end organs [7, 15]. The onset of action of MEV (after intramuscular injection) is 2 to 5 min, and its elimination half-life is 0.5 to 2 h [10].

Arterial vasospasm, gastrointestinal problems (nausea, emesis, and diarrhea), neurological complications (seizures, peripheral paresthesias, and coma), and respiratory difficulties were reported in children and adults [1]. Despite similarities, it is important to note that ergotism can manifest quite differently in neonates than in adults. Adults generally develop hypertension, but infants more commonly become hypotensive. Respiratory failure, oliguria, and seizures are rare in adults, but common in newborns [4].

MEV is used for the prevention and control of postpartum hemorrhage [14]. It is usually kept in labor rooms for immediate parenteral use during the last stage of labor. Most instances of neonatal MEV poisoning have

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A. Y. Bas · N. Demirel  
Department of Neonatology, Etlik Zubeyde Hanım  
Maternity and Teaching Hospital,  
Ankara, Turkey

A. Soysal  
Department of Pediatric Infectious Disease,  
Marmara University School of Medicine,  
Ankara, Turkey

K. Arslan  
Pediatrician, Inegol Community Hospital,  
Ankara, Turkey

U. Dilmen  
Department of Neonatology,  
Zekai Tahir Burak Maternity and Teaching Hospital,  
Ankara, Turkey

A. Y. Bas (✉)  
Etlik Zubeyde Hanım Kadın Doğum  
Eğitim ve Araştırma Hastanesi,  
Yeni Etlik Caddesi 55, Etlik,  
06010 Ankara, Turkey  
e-mail: yagmur32@yahoo.com

occurred when infants inadvertently receive the ergot derivatives instead of vitamin K or naloxane [8].

We report a series of 12 newborn patients of parenteral MEV poisoning who presented with sepsis-like symptoms on the same day. Not all the reported previous cases were due to perinatal events. Our series is the largest intramuscular MEV poisoning in newborns reported from a single center. The present study differs from the former articles since MEV intoxication emerged as mimicking a sepsis outbreak.

### Patients' information

All 12 newborns were delivered by the same midwives in a local country hospital (in Bursa, Turkey) on the same day (July 1, 2009) and developed sepsis-like symptoms and encephalopathy within 2–6 h of life. Demographic features, clinical data and course, laboratory findings, management, and results were noted in detail.

Birth weight, type of delivery, gender, age on admission, complaints at admission, needs for resuscitation in the delivery room, presence of perinatal asphyxia, birth trauma, maternal fever, chorioamnionitis, maternal diabetes, and gestational hypertension were recorded.

Lethargy, feeding intolerance, cyanosis, convulsion, peripheral circulatory abnormalities (assessed by skin color of extremities and acral edema), hypotension (blood pressure <10th percentile) [12], renal insufficiency (serum creatinine >1.5 mg/dl and/or urine output <1 cm<sup>3</sup>/kg/h) [13], and apnea (requiring mechanical ventilation support) were noted.

Acidosis was defined as a pH <7.2, hypercarbia was defined as a partial pressure of carbon dioxide (PaCO<sub>2</sub>) >50 mmHg, and hypoxemia was defined as a partial pressure of oxygen (P<sub>a</sub>O<sub>2</sub>) <50 mmHg with a fraction of inspired oxygen (FiO<sub>2</sub>) >0.6–0.7. Arterial oxygen levels between 88% and 95% were regarded normal. The indication for continuous positive airway pressure (CPAP) was prolonged apnea with significant CO<sub>2</sub> retention [2].

*Laboratory and radiological studies* Cultures from different surfaces in the delivery room of the local hospital were obtained initially since the clinical presentation resembled a sepsis outbreak. On admission to the referred hospital, a complete blood count, blood smear, and biochemical parameters including, plasma glucose, electrolytes, blood urea nitrogen, creatinine, liver transaminases, arterial blood gas analysis, coagulation test results, and chest x-rays were assessed in all patients.

All cases underwent cerebrospinal fluid (CSF) sampling for evaluation including total and differential cell count, biochemical studies, and microscopic evaluation after

Gram, India ink, staining. Polymerase chain reaction (PCR) studies for adenovirus, echovirus, coxsackie virus, and herpes simplex virus serotypes were performed in CSF of all cases in a reference laboratory. Results of blood culture and acute-phase reactants were also assessed. All patients received antibiotics as soon as possible.

Additional tests including cranial ultrasonography and electroencephalography (EEG) were performed in all patients with seizures.

*Statistical analysis* Statistical analyses were performed using SPSS 16.0 for Windows. Data were expressed as mean (SD).

### Results

Twelve newborns were delivered by the same midwives in a local country hospital (in Bursa, Turkey) on the same day (July 1, 2009) and developed sepsis-like symptoms and/or encephalopathy within 2–6 h of life. The delivery room was closed immediately due to the suspected sepsis outbreak, and all cases were referred to a tertiary neonatal intensive care unit.

- (a) Demographic features: The mean age of patients at admission was 3.6±1.2 h (range, 2–6 h), mean gestational age was 38.7±1.5 weeks (range, 37–42 weeks), and birth weight was 3,192±322 g (range, 2,650–3,700 g). Of the 12 newborns, seven were male and five were female. Eight of infants were born after uncomplicated vaginal deliveries, while four infants were delivered by cesarean section. None had a history of premature rupture of membranes, maternal fever, or signs of infection at gestation. Mean hospital stay was 6.7±1.5 days (range, 5–10 days). Demographic features of patients are presented in Table 1.
- (b) Patients' clinical data: The first symptoms were lethargy, seizure, feeding intolerance, and hypoventilation (cyanosis and/or apnea) in most cases. Seizures occurred in nine of 12 (75%) infants and recurred during the first 6 h. Eight of 12 infants (66.6%) had difficulty in feeding. Other notable transient neurological effects included lethargy (*n*, 5; 41.7%) and irritability (*n*, 3; 25%).

Two patients (case 1 and case 2) required CPAP. Most of the cyanotic (*n*, 7; 58.3%) required oxygen to maintain oxygen saturation over 88%, but none of the cases required endotracheal intubation.

Of the all cases, seven (58.3%) had peripheral circulatory abnormalities. Acral bluish discoloration and edema were noted in these infants. Renal

**Table 1** Demographic features and clinical findings of ergotamine toxicity in infants

Case number	1	2	3	4	5	6	7	8	9	10	11	12
Age at admission (h)	2	4	2	3	3	4	6	4	5	5	3	3
Gestational age (weeks)	39	38	37	41	38	37	38	38	40	39	38	42
Birth weight (g)	3,180	3,400	2,650	3,160	3,580	2,800	3,300	3,700	3,100	3,500	3,090	2,850
Gender	M	M	F	F	M	F	F	M	F	M	F	F
Sings and symptoms												
Apnea	+	+	-	-	-	-	-	+	-	-	-	-
Cyanosis	+	+	-	+	+	-	-	+	-	+	-	+
Seizure	+	+	+	-	-	+	+	+	+	+	+	-
Irritability	-	-	-	-	+	+	-	-	+	-	-	-
Lethargy	-	-	+	+	-	-	+	-	-	-	+	+
Poor feeding	+	+	+	+	-	-	+	+	-	-	+	+
Peripheral circulatory abnormalities	+	+	-	+	+	-	+	+	-	-	-	+
Hypotension	+	+	-	-	-	-	+	+	-	-	-	-
Clinical characteristics												
Oxygen requirement	+	+	-	+	+	-	-	+	-	+	-	+
Nasal CPAP	+	+	-	-	-	-	-	-	-	-	-	-
Seizure type	Clonic	Clonic	Tonic	-	-	Clonic	Tonic	Tonic	Clonic	Clonic	Tonic	-
Renal function	N	N	N	N	N	N	Impaired	Impaired	N	N	N	N
Laboratory findings												
Arterial blood gas analysis	Hypoxemia hypercarbia	Hypoxemia hypercarbia	N	Hypoxemia	Hypoxemia	N	N	Hypoxemia	N	Hypoxemia	N	Hypoxemia
Serum creatinine level (mg/dl)	N	N	N	N	N	N	1.6	1.7	N	N	N	N
Oliguria	-	-	-	-	-	-	+	+	-	-	-	-
EEG	N	N	N	N	N	N	N	N	N	N	N	N
Treatment	Phenob, Inotrop	Phenob, Inotrop	Phenob, Inotrop	Phenob	Phenob	Phenob	Phenob, Inotrop	Phenob, Inotrop	Phenob	Phenob	Phenob	Phenob
Hospitalization length (day)	10	8	6	5	5	7	7	7	8	6	6	5
Outcome	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery

F female, M male, Nasal CPAP nasal continuous positive airway pressure, EEG electroencephalography, Phenob phenobarbitone, Inotrop inotropic agent, N normal

dysfunction characterized by oliguria was noted in cases 7 and 8. There was hypotension in four cases (33.3%). Patient's clinical data are presented in Table 1.

- (c) Laboratory and radiological findings: All patients had complete blood count, acute phase reactant levels, biochemical parameters including plasma glucose, electrolyte, and transaminase levels, and coagulation tests within normal range. In cases 7 and 8, serum creatinine levels were 1.6 and 1.7 mg/dl, respectively. Renal function tests in the remaining ten patients were normal. Arterial blood gas analysis in case 1 revealed a pH of 7.20, a  $PCO_2$  of 59 mmHg, a  $PO_2$  of 44 mmHg, a  $HCO_3$  level of 19.8 mEq/L, and a base deficit of -5.7. Case 2 had a pH of 7.18, a  $PCO_2$  of 60.7 mmHg, a  $PO_2$  of 42 mmHg, a  $HCO_3$  level of 23.1, and a base deficit of -2.3. Blood gas analysis revealed hypoxemia except cases 3, 6, 7, 9, and 11 (Table 1).

CSF analysis including PCR studies was normal in all cases. Blood and CSF cultures of all patients and surface cultures of the labor ward were negative.

Chest x-rays of all patients were normal. Cranial ultrasonography and EEG studies revealed no abnormalities in patients with seizures. Laboratory findings are summarized in Table 1.

- (d) Treatment and outcome: Empirical antibiotic treatment was commenced to all patients at admission. None of the patients needed ventilator support or oxygen therapy by 48 h. Renal impairment was treated by appropriate fluid infusion and inotropic agents. Elevated urea and creatinine levels in two infants returned to normal within 3 days. Inotropic agents were required in cases 1, 2, 7, and 8, who were also hypotensive and were discontinued by the end of the second day.

Antibiotic treatment was discontinued when culture results yielded no microorganisms. Cases with seizures received phenobarbitone and seizure activity abated in these cases by 48 h except case 3 and case 11, which diminished by 72 h.

The delivery room history was reinquired, and this revealed an inadvertent medication by the midwives, who did not report the mistake with a worry of litigation. There was no documentation of inadvertent MEV administration in the referral letters of our cases. We reported our findings to the appropriate governmental agency.

Twelve cases of definite accidental administration of MEV were identified. The mistake was discovered virtually 3 days after the midwives administered Methergine® inadvertently to all infants immediately after delivery instead of vitamin K in the delivery room. Methergine® is available in ampoules of 1 mL, containing 0.2 mg MEV maleate. It was given intramuscularly

in a dose of 0.2 mg in each patient. Unfortunately, we noticed that methergine ampoules were next to the vitamin K ampoules on the same shelf.

Phenobarbitone treatment was discontinued at discharge in all patients. All patients were clinically well, and also, physical and neurological examinations were entirely normal at the time of discharge from the hospital.

## Discussion

The features of ergot toxicity are caused predominantly by alteration in vascular tone, affecting circulation to many different end organs. Several ergot alkaloids are available in different forms. MEV is a semi-synthetic ergot derivative used to treat and prevent postpartum uterine hemorrhage. Ergot toxicity in the newborn is almost exclusively iatrogenic [7, 15].

The symptoms of ergot poisoning result from varied pathophysiologic mechanisms, but most of the effects are attributed to the direct effects of ischemia caused by vasoconstriction. The most immediately life-threatening event in neonatal intoxication is respiratory failure [4]. The ventilation perfusion mismatch resulting from pulmonary vasoconstriction may explain the respiratory signs. Signs of central nervous system ischemia may appear and are believed to result from the direct action of ergot on the cortical neurons and to a decrease in cerebral blood flow [14]. Central nervous system toxicity may include seizures, lethargy, and irritability [7]. Hypoperfusion and transient ischemia could cause temporary renal dysfunction [4]. Ergot poisoning has been noted to compromise mesenteric blood flow and may cause localized ischemic necrosis of the intestine and feeding intolerance [16].

The time frame during the development of symptoms is not well described, except for respiratory failure and seizures, which occur for fewer than 6 and 3 h, respectively [1, 4]. The presented patients became symptomatic within the first few hours after birth.

Aeby et al. [1] reviewed 34 cases of ergot poisoning in children that occurred in Belgium between 1969 and 1999. Fourteen patients were newborn, and in 12 cases, mothers inadvertently administered oral methylergometrine instead of vitamins. Intramuscular exposure was associated with severe complications, including apnea, coma, and convulsions. Complications following inadvertent oral administration are tolerated better.

Most serious cases of neonatal intoxication involve the parenteral administration of an ergot to a newborn. Bangh et al. [4] reviewed 55 cases (40 parenteral and 15 oral) of neonatal ergot poisoning in literature, between 1966 and 2003. Respiratory distress (55%), pallor/mottling/cyanosis

(49%), seizures (47%), intubation requirement (47%), oliguria/renal insufficiency (18%), and death (5%) were prominent features.

Dargaville et al. [7] documented main features of parenteral ergometrine toxicity in seven newborn infants at the Royal Children's Hospital between 1970 and 1996. The major features of toxicity were encephalopathy (100%), peripheral vascular disturbances (100%), seizures (100%), artificial ventilation need (86%), hypoxemia (43%), feeding intolerance (43%), and renal impairment (43%).

We report a series of 12 newborn patients of parenteral MEV poisoning. Nine of 12 (75%) infants had seizures, while eight (66.6%) had feeding intolerance. Other notable transient neurological effects included cyanosis (58.3%), lethargy (41.7%), respiratory distress (58.3%), peripheral circulatory abnormalities (58.3%), hypotension (33.3%), and irritability (25%). Temporary renal dysfunction was noted in two cases (16.7%), characterized by oliguria and elevated serum creatinine levels which returned to normal within 3 days. None of the patients required endotracheal intubation, and there was no mortality.

Clinical findings in ergot toxicity are nonspecific and cannot be distinguished from infectious disease or neonatal encephalopathy [11]. Fortunately, iatrogenic ergot toxicity, which is a real diagnostic problem, occurs infrequently. The cases presented here were diagnosed as sepsis/neonatal encephalopathy at time of admission, and ergot toxicity was not recognized early in the course of the disease.

Urine toxicology tests are generally inadequate in testing ergot toxicity, and standard clinical screening in urine is not useful at all. Serum ergot levels are not recommended because they are not readily available and have not been correlated with toxicity [10]. However, a general unknown toxicological screening procedure in urine or blood samples is the most appropriate approach to reveal iatrogenic exposure. Since a newborn should not receive any ergot derivative, the finding of ergot alkaloids at whatever concentration is precious information. In cases ergot poisoning is suspected at a later time, hair analysis can be useful in retrospective screening [9].

Treatment is targeted to symptoms. If evidence of severe vasoconstriction appears, administration of sodium nitropruside should be considered. Once the infant is stabilized, the continuing management essentially consists of supportive measures such as ventilatory assistance, seizure control, and intravenous therapy [7, 10]. With appropriate supportive care, full recovery is expected, as in the cases reported here.

Prompt diagnosis of accidental MEV administration is critical for treatment and avoidance of unnecessary laboratory investigations, invasive procedures, and inappropriate treatment modalities. It is important to be highly suspicious in newborns who are vigorous at birth but subsequently develop unexplained signs of sepsis and encephalopathy.

In conclusion, a thorough history of events that occurred perinatally and at the delivery table is the cornerstone of diagnosis for MEV toxicity. Meticulous attention in every detail would be the best way to prevent malpractice. Strict preventive guidelines and educational efforts are crucial for reducing medico-legal events.

**Conflicts of interest** None.

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