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Clinical manifestations and neurodevelopmental outcome following an event of accidental intramuscular injection of atracurium in newborns

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Abstract Pediatric populations are at risk for medication errors that may be associated with mortality and disability. The purpose of this study was to describe the clinical manifestations of seven newborns following an event of accidental intramuscular injection of atracurium and to assess the impact on neurodevelopmental outcome. This study enrolled seven newborns who were accidentally administered 10 mg of atracurium, equivalent to 2.6–3.3 mg/kg, in a local perinatal clinic. Accident reports and hospital records were reviewed to obtain the history and medical data for the event. The survivors were prospectively

examined for their growth, health and neurodevelopment until 24 months of age. All newborns showed immediate apnea and cyanosis requiring resuscitation after atracurium injection and presented with respiratory failure and flaccid paralysis on arrival for emergency medical services. One newborn was asystolic despite resuscitation and died of multiple organ failure. Of the five survivors available for follow-up, all achieved favorable growth outcomes. However, four showed mild to significant delay in development; and two manifested mild hypomyelination of cerebral white matter on the brain magnetic resonance imaging. **Conclusion:** Newborns accidentally injected with high doses of atracurium are at risk of death and neurodevelopmental delay. The serious clinical manifestations, developmental delay and cerebral hypomyelination were most likely due to insufficient immediate respiratory assistance following atracurium injection.

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Abbreviations MRI: Magnetic resonance imaging · EEG:
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Introduction

Pediatric populations are at significant risk for medication errors partly because children can not communicate well and because the appropriate dose is usually not clear [11]. While some errors might be minor, those associated with mortality and disability are a major burden to patients and their families and also significantly increase health care costs and can be a source of litigation [3, 19].

Atracurium is a neuromuscular blockade widely used to provide muscle relaxation during surgery and in critically ill patients [9, 27]. Pharmacokinetic studies have shown that below the usual therapeutic dose (0.5 mg/kg for pediatric patients and 0.6 mg/kg for adult patients), atracurium produces maximum neuromuscular blocking effect 3–

5 min following injection, and recovery is generally 95% complete 1 h postinjection [9, 12, 24, 25]. High doses of atracurium tend to prolong the duration of action and increase the risk of adverse reactions such as cardiovascular collapse and seizure activity [14, 23]. The toxic level that leads to circulatory depression and seizure activity has been well established in animals [4, 13, 15, 28], but it remains unclear in humans. Previous case studies of atracurium overdose on ventilated infants reported minimal clinical effects [5, 8]. Association of seizures and atracurium overdose has been reported in adult patients who had other comorbidities such as head trauma, hepatic failure and uremia [21, 22, 35].

High doses of atracurium (10 mg, equivalent to 2.6–3.3 mg/kg) were mistakenly injected instead of hepatitis B vaccine in seven newborns in the nursery of a local perinatal clinic in Taiwan. One newborn died and the others required intensive care because of acute hypoxia and cardiopulmonary failure. A multidisciplinary team was organized to prospectively follow up the survivors' growth, health and neurodevelopment until 24 months of age. The aims of this study were therefore to assess the clinical manifestations of the seven newborns following accidental injection of atracurium and to examine the impact on neurodevelopmental outcome.

Subjects and methods

We enrolled seven newborns (cases A, B, C, D, E, F and G) who were involved in the medical accident of atracurium injection at age 4–5 days in a local perinatal clinic in Taipei, Taiwan, on November 29, 2002. All infants were born at term after uncomplicated pregnancies with 1- and 5-min Apgar scores of ≥ 8 and had normal newborn examinations. Their parents all had educational levels of at least high school. This study was approved by the Institutional Ethics Committee of the National Taiwan University Hospital, Taipei, Taiwan. Informed consent was obtained from the parents of all infants before participation in the study. Case F was lost to follow-up because of difficulty in maintaining parental compliance with the appointment schedule.

Review of patient records

All records associated with the infants, including accident reports, prehospital run sheets, emergency records and hospital records were reviewed to obtain the information of history and clinical manifestations. The data included course of event, physical examination, initial arterial blood gas values, laboratory data, echocardiography, renal ultrasonography and electroencephalography (EEG).

Follow-up schedule and outcome assessments

The survivors were prospectively examined for their growth, health and neurodevelopment at the Department

of Pediatrics, National Taiwan University Hospital. Growth, health and development were assessed at 6, 12, 18 and 24 months of age. Brain magnetic resonance imaging (MRI) examination was conducted at 16 months of age.

Growth measures included weight, height and head circumference. Health measures included number and diagnosis for rehospitalization. Development was assessed by an experienced psychologist using the Bayley Scales of Infant Development, 2nd edition (BSID-II) [2]. The BSID-II contains a motor scale (111 items) and a mental scale (178 items) that measure infant development from 1–42 months of age. The assessment has acceptable levels of reliability and validity when used on Taiwanese infants [6, 16, 17]. Because no norm has been established for the BSID-II in Taiwan, the motor and mental raw score were each transformed into a standard score (z score) using the standards published in our previous study [16]. Developmental outcome was categorized as normal ($z > -1$), mildly delayed (z between -1 and -2) or significantly delayed ($z < -2$) [2].

The MRI scans were performed using a 1.5-T scanner (Sonata; Siemens, Erlangen, Germany). Fast-spin echo (FSE) T2-weighted images in the axial plane were obtained with the following parameters: TR/effective TE=5,300/93 ms, echo train length of 11, matrix size of 384×512, field of view 16×16 to 18×18 cm, slice thickness of 4 mm with gap of 1 mm, and one acquisition. All images were assessed by an experienced radiologist (S.P.).

Results

Acute phase

Review of history revealed that the infants in the perinatal clinic were scheduled to have hepatitis B vaccination on November 29, 2002, which was the fourth or fifth day after birth. In Taiwan, hepatitis B vaccination is obligatory for newborns prior to hospital discharge. In this case, the muscle relaxant atracurium was stored in the same refrigerator with the hepatitis B vaccine in the nursery. Atracurium has not been used by this perinatal clinic but was brought in privately about 6 months before the accident by a nurse anesthetist who purported to use it for anesthesia in the operation room. Because the operating room is situated on the same floor as the nursery, the nurse anesthetist placed atracurium in the refrigerator that stored the hepatitis B vaccine for her own convenience. The two drugs were from different companies and had no similarity in packages, vials and labels. However, a nurse in the nursery mistook the muscle relaxant for the vaccine and sequentially administered 1 c.c. (10 mg, equivalent to 2.6–3.3 mg/kg) intramuscularly to seven individual infants. The nurse who administered atracurium had worked at the perinatal clinic for five months since graduation from a nursing college. The nursery consisted of 30 beds and was staffed by one pediatrician and 10 nurses. The nurses worked on 8-h shifts under the supervision of a head nurse.

The infants showed apnea, bradycardia and cyanosis within minutes of the accidental injection and cardiopulmonary resuscitation was immediately applied. Due to persistent respiratory failure, intubation was performed on the infants by the pediatrician and the nurse anesthetist who was qualified for pediatric cardiopulmonary resuscitation. This was followed by assisted ventilation alternating with ambu-bagging because only two pediatric-sized ambu-bags were available on site. Meanwhile, the perinatal clinic had phoned the Fire Bureau of the county to assist in transportation. Upon arrival of the ambulance, one case (G) manifested significant respiratory failure and re-intubation was attempted. All infants were subsequently transported via ambulance to three nearby hospitals for primary emergency care. The arrival time at the emergency services was 1 h post-injection. Due to insufficient ventilators, two cases (A and F) were then transferred to other hospitals, so that the arrival time at the second emergency care facilities was 2–2.5 h post-injection.

On arrival in the emergency department, all infants were apneic and flaccid. One case (A) presented mild hypotension, one case (F) showed bradycardia and unmeasurable blood pressure, and one case (G) was pulseless (Table 1). The first blood sampling was performed 1.5–5 h post-injection. The arterial blood gas analysis revealed respiratory acidosis combined with metabolic acidosis in four

cases (A, E, F and G) and mild respiratory alkalosis in one case (D), which might be related to blood sampling after ambu-bagging or ventilator therapy. Laboratory data showed hyperglycemia in all and a borderline elevation of creatine kinase level in five cases (A, C, D, E and F). Sodium bicarbonate, epinephrine and dopamine were initially used; neostigmin and atropine were subsequently administered as antidotes after atracurium was identified as the target injection drug. A 2-h attempt at rigorous resuscitation was unsuccessful in one case (G), and the patient ultimately died of multiple organ failure. The remaining infants survived but required mechanical ventilation (mean duration 26.7 h, range 5–96 h), oxygen therapy (mean duration 3.3 days, range 2–6 days) and hospitalization (mean duration 9.8 days, range 7–12 days).

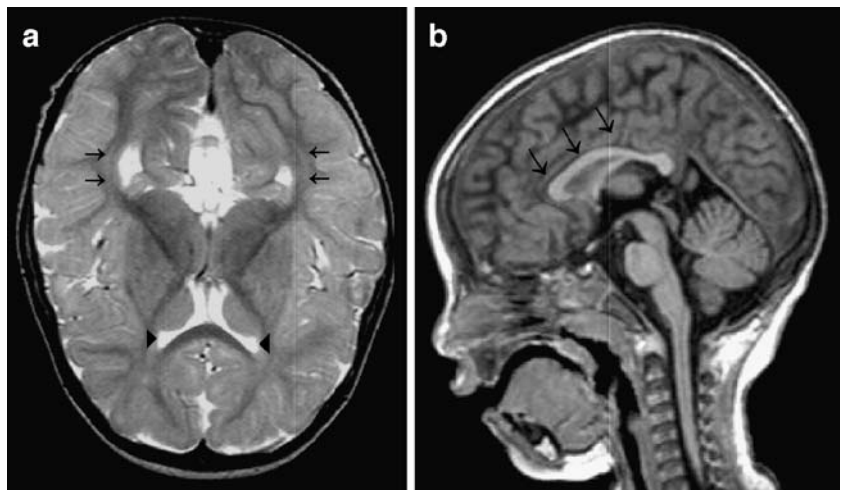
During hospitalization, the echocardiographic examination showed mild tricuspid regurgitation in two cases (B and E), patent foramen ovalae and arrhythmia in one case (F), and normal findings in three cases. The renal ultrasonographic examination revealed poor cortico-medullary differentiation over the upper pole of the right kidney suggesting acute renal failure in one case (F) and normal findings in the remainder. The EEG examination revealed paroxysmal discharge with diffuse low voltage slow waves in one case (B), focal spike waves at right

Table 1 Characteristics of the infants sustaining accidental injection of atracurium ($n=7$)

	Survivors						Non-survivor
	Case A	Case B	Case C	Case D	Case E	Case F	Case G
Gender	Female	Male	Female	Female	Female	Female	Female
Gestational age (wk)	40	40	38	41	40	38	41
Birth weight (g)	3,415	3,775	3,890	3,075	3,110	2,835	3,165
Vital signs on arrival at emergency care							
HR (bpm)	173	118	146	131	122	60	0
Systolic/diastolic BP (mmHg)	55/36	63/33	87/41	87/42	70/30	Unmeasurable	0
Initial blood sampling (h post-injection)	1.5	5	2	2	2	3	2
Arterial blood gas values							
pH	6.89	7.37	7.30	7.39	7.07	6.58	6.44
Paco ₂ (mmHg)	73.9	43.7	46.9	15.5	63.4	150.3	80.1
Pao ₂ (mmHg)	43	72.9	52.3	201	12.4	236.9	81.2
Bicarbonate (mmol/l)	14.2	24.9	22.3	9.4	17.9	13.1	5.3
Base excess (mmol/l)	-19.5	-0.3	-4.2	-15.8	-12.2	-	-
Laboratory data							
Sodium (mEq/l)	137	132	145	139	149	148	134
Potassium (mEq/l)	5.0	4.8	3.5	3.5	3.1	3.1	13.1
BUN (mg/dl)	4	3	5	5	3	7	9
Creatinine (mg/dl)	0.4	0.5	0.4	0.5	0.4	0.4	0.7
AST (IU/l)	30	25	52	31	18	38	87
CK (IU/l)	525	ND	755	703	438	596	ND
CK-MB (U/l)	76	ND	253	98	62	42	ND
Blood glucose (mg/dl)	334	695	212	240	169	385	700
EEG findings	Normal	Diffuse slow waves	Focal spike waves	Normal	Focal spike waves	Normal	-

HR Heart rate, BP blood pressure, ND not done, BUN blood urea nitrogen, AST aspartate aminotransferase, CK creatine kinase isoenzyme

Fig. 1 Lesions identified in case A on MRI at 16 months of age. **a** Axial fast spin-echo T2-weighted image (TR/effective TE=5,300/93 ms) reveals hypomyelination at occipital central parenchyma on both sides (*arrows*). Both frontal horns are prominent and square in shape (*arrowheads*). **b** Magnetization-prepared rapid gradient echo image (TR/TE/TI=1,900/3.9/1,100 ms) in the sagittal plane shows diffusely thin body of the corpus callosum (*arrows*) of the corpus callosum



temporal-parietal areas in one case (C), focal spike waves at right central-parietal areas in one case (E), and normal findings in three.

Follow-up

Of the five survivors regularly examined by our team, the growth measures at all assessment times during follow-up were within the 20–97th percentile of the population of the same age in Taiwan. Three were rehospitalized, mainly in the first year of age: once in case A for pneumonia, four times in case B for acute bronchiolitis and bronchopneumonia, and once in case E for upper-respiratory-tract infection.

Brain MRI performed at 16 months of age illustrated abnormalities in two cases (A and B) and no abnormal findings in the remainder. Case A showed ventricular enlargement, mild hypomyelination at bilateral parietal and occipital central white matter (Fig. 1a) and diffusely thin body of the corpus callosum (Fig. 1b). Case B manifested mild hypomyelination at bilateral parietal and occipital central white matter.

The series of BSID-II assessments revealed significant delay in motor development in Case A from 12 months onward and mild delay in mental development from 18 months onward. Case B exhibited mild delay in motor development at 12 and 24 months of age, together with mild delay in mental development at 12 months of age. Cases C and E manifested transient deterioration in developmental performance: case C had mildly delayed motor development at 12 months of age, followed by mildly delayed mental development at 18 months of age; while case E had mildly delayed motor development at 24 months of age. Only case D showed normal motor and mental development throughout the follow-up period.

As for the developmental intervention, all infants received counseling and home program instruction following each developmental assessment. Only one child (case A) received physical, occupational and speech therapy after 9 months of age.

Discussion

This study is the first report on clinical manifestations and neurodevelopmental outcome of newborns following an event of accidental intramuscular injection of high doses of atracurium. The event resulted in one death and six requiring intensive care services. Of the five survivors available for follow-up, all achieved favorable growth outcomes during 24 months of age. However, four infants showed mild to significant delay in motor or mental development; and two of them manifested mild hypomyelination of cerebral white matter on the MRI. The results indicate that newborns inadvertently administered high doses of atracurium are at risk of mortality and neurodevelopmental delay.

Pediatric patients have been reported to pose unique challenges to the system of ordering, dispensing, administering and monitoring medications [11]. Analysis of the causes of this medical event revealed that errors occurred at the stage of drug dispensing and administering. Negligence was noted in the nurse anesthetist who placed the potentially lethal drug atracurium in an improper place and in the nurse who administered the wrong medication. In addition, errors also arose from the perinatal clinic's failure to establish secure medical procedures to safeguard patients' safety. The results of this study demonstrate that medication errors can endanger patients' lives, cause mental or physical injuries, and stress families. Strategies to prevent such medication errors may emphasize education of medical practitioners, improved dissemination and enforcement of practice guidelines, and development of better mechanisms for identifying negligent behavior and instituting appropriate disciplinary actions.

The clinical features manifested by these newborns were more serious than those documented in previous case studies of atracurium overdose [5, 8]. All infants showed immediate apnea and cyanosis requiring resuscitation and presented respiratory failure and skeletal muscle paralysis on arrival at emergency medical facilities. One child was asystolic and ultimately died of multiple organ failure. In contrast, previous case studies of atracurium overdose in

infants showed minimal clinical responses. For example, Durcan and Carter documented a dose of 5.1 mg/kg atracurium via intravenous bolus injection on a 3-week-old infant, who showed skin flushing, hypotension and tachycardia, but the symptoms subsided after medical management [8]. Charlton et al. reported a dose of 37 mg atracurium over 75 min in a 2-month-old infant who showed skin flushing only [5].

The considerably insignificant clinical effects in previous studies might be due to the occurrence of atracurium overdose during routine anesthesia, so that the infants were instantly intubated and monitored in an intensive therapy unit. The medication errors reported in this study occurred in a local perinatal clinic, and the newborns needed to be transferred to other hospitals for intensive care services. Prior to transportation, the infants might have received insufficient ambu-bagging in the field such that one child (case G) exhibited severe respiratory failure and ultimately died. Furthermore, the duration of transportation was about 1 h for most infants and extended to 2–2.5 h in two infants; the latter two developed either acute renal failure (case F) or mental and motor delay (case A). While the information concerning the timing and management of this event was mainly abstracted from prehospital runsheets, emergency records and the on-site pediatrician's recall, there were inherent ambiguities in assessing the quality of prehospital resuscitation. Nevertheless, the clinical manifestations concerning respiratory acidosis, hyperglycemia, renal insufficiency, cardiac arrest and multiple organ failure were characteristic features of hypoxia [20, 33], that were likely due to inadequately assisted ventilation during muscle relaxation. Our findings therefore highlight the importance of immediate establishment of ventilation and perfusion in the field after mistaken atracurium administration.

The follow-up data revealed developmental delay in four survivors, of which two manifested hypomyelination on the MRI. Two infants (cases A and B) showed mild to significant delay in motor development and mild delay in mental development at 24 months of age. Meanwhile, their brain MRI findings at 16 months of age showed mild hypomyelination in periventricular white matter. In contrast, the two infants (cases C and E) with transient developmental delay and the one infant (case D) with normal development exhibited no abnormal findings on the MRI at 16 months of age. These data support the results of several previous studies that delayed myelination in white matter during infancy is associated with retarded psychomotor development [10, 30, 32]. A continued developmental follow-up of the surviving infants with accidental injection of atracurium is necessary to determine if this adverse event will affect the long-term outcome.

The association of delayed myelination with accidental injection of atracurium in newborns is a significant finding. The periventricular white matter lesions in case A were characterized by mild hypomyelination in the periventricular white matter, ventriculomegaly and thinning of the corpus callosum, while those of case B were characterized by mild hypomyelination in the periventricular white matter. The anatomical distribution of white matter lesions

is not in keeping with the common sites of hypoxic-ischemic encephalopathy in term infants, since these sites commonly involve the hemispheres, the basal ganglia and the parasagittal subcortical structures [1, 26, 29]. The pattern of white matter lesions seems to conform better with periventricular white matter lesions, also called periventricular leukomalacia, which are often observed in preterm infants after hypoxic-ischemic insult [7, 10]. Some studies have demonstrated that periventricular white matter lesions are rare in term infants and such neural lesions are more likely caused by mild, prolonged hypoxia [18, 31, 34]. Our results suggest that the infants surviving atracurium injection might undergo mild hypoxia over an extended period of time prior to arrival in intensive care.

In summary, the cases reported in this study demonstrate that inadvertent administration of high doses of atracurium can have very serious or fatal consequences for newborns. The serious clinical manifestations, developmental delay and cerebral hypomyelination were most likely due to insufficient immediate respiratory assistance following atracurium injection. The comprehensive examination of the clinical course and outcome of this adverse event provides important information to help design preventive strategies to reduce such medication errors.

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