Theophylline Overdose in Premature Neonate: A Case Report and Review of Pharmacokinetics

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ABSTRACT

Theophylline is well-accepted in neonatal medicine for its efficacy in treating apneas of prematurity. However, due to its narrow therapeutic index, decreased drug elimination capacity and limitations of enhanced elimination methods in premature newborns, inadvertent overdoses in this age group can be difficult to manage. We report a case of therapeutic misadventure of a 30-week-old infant who received and overdose of aminophylline for apnea of prematurity. The patient was symptomatic with tachycardia, agitation, vomiting, hyperglycemia and diuresis. He received an exchange transfusion 9 hours after the overdose and had progressive resolution of symptoms. The pharmacokinetics of theophylline in cases of overdose in the neonates is reviewed.

Keywords: Adverse drug reaction; drug overdose; neonates; medication errors; theophylline

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Theophylline, a xanthine derivative, is widely used in the treatment of apnea of prematurity. Its actions as both a direct stimulant of the central respiratory drive, as well as aiding in the contractility of the diaphragm, rendered the drug a valuable tool of treatment. However, its narrow therapeutic range, together with the variable metabolism due to ontogeny of the primary metabolic pathway in infants, the cytochrome p450 and various other drug-drug and drug-disease interactions, made theophylline a drug which is at high risk for iatrogenic toxicity. We report here a case of medication error in a premature newborn, resulting in theophylline toxicity which was successfully treated with an exchange transfusion.

CASE REPORT

A 1,550 gram female neonate born to a 26 years old G1P1A0 mother with estimated gestational age of 30 +5 weeks by date and Apgars of 10^{1}, 10^{5} was transferred to the newborn nursery for observation due to low birth weight. Initial physical examination showed a pink, active, female infant with respiratory rate of 50/minute and oxygen saturation of 99-100% in room air. No retraction or respiratory distress was noted.

At 8 hours of age, the patient began developing intermittent cyanosis and apnea. Physical examination at that time showed central apnea and central cyanosis. The patient was diagnosed with apnea of prematurity and was started on aminophylline 3mg in 5ml of 5% dextrose given as intravenous drip over 1 hour. Subsequently, after the completion of the IV medication, the patient was noted to be agitated, crying, and had several episodes of vomiting. It was discovered at that time that the patient actually received aminophylline 3ml (equivalent to 75 mg). Physical examination at that time showed an agitated, crying infant with heart rate of 190-230 beats/minute and vomiting. Theophylline level was 30.77 mg/L (3 hrs after the drug administration). Other laboratory investigations were Na137.K4.5.CL105 HCO_3 19 and serum glucose of 192 mg/dL.

At 4 hours after the drug administration (12 hours of life), the patient promptly received an exchange transfusion with 120 ml of blood. The theophylline level prior to the exchange was 30.77 mg/L. She experienced no complications. Subsequently, the heart rate began to decrease to 160-180 beats/min, and the vomiting subsided. Theophylline level post-exchange was 41.23 mg/L. The patient continued to receive supportive care with no other complications and was discharged on day 30^{th} of life with the weight of 2,100 gm.

A summary of laboratory values obtained during the hospital stay are shown in the following Table 1.

TABLE 1. Laboratory investigations.

Age	Blood glucose	Electrolyte $Na^+/K^+/Cl^-/HCO_3$	Theophylline level (mg/L)
3 hours (pre exchange)	192	135/4.5/105/19	30.77
Post exchange	168	135/4.7/106/12	41.23
29 hours	80-150	135/3.8/105/14.7	34.34

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TABLE 2. Theophylline clearance and half-life according to age.

Clinical situation	Clearance	Half-life (hr)
Neonatal	0.02-0.63 mL/kg/min	24-36(7)
Children (1-12 years)	1.45 mL/kg/min	1.5-9.5
Adults (>12 years)	0.65 mL/kg/min	8.3

DISCUSSION

Aminophylline, theophylline, and caffeine are xanthine derivatives. As theophylline is well absorbed in the gastrointestinal tract, it is considered to have 100% bioavailability in the oral form. The intravenous form, aminophylline, is an ethylenediamine salt form of theophylline and is consi-dered to have 80% drug availability. In normal individuals, theophylline undergoes hepatic metabolism via cytochrome p450 isoenzymes 2E1, 1A2 and 3A4 to form 3-methy-lxanthine, 1-methyl uric acid, and 1,3-dimethyluric acid which is the active metabolite. Renal elimination accounts for only about 10% of theophylline dose. At sub-therapeutic concentrations, hepatic elimination of theophylline follows first order kinetics. However, at near and supra-therapeutic concentrations, theophylline can exhibit zero order kinetics, making the elimination half-life much more prolonged.[1,2]

In neonates, cytochrome p450 isoenzyme activities are relatively inactive. As a result, theophylline undergoes n-methylation to form the metabolite, caffeine, in significant amounts. It is estimated that well over 25% of the dose is metabolized into caffeine that is, in turn, excreted unchanged in the urine. Overall, renal elimination can account for up to 50% of the theophylline dose in neonates. Thus, renal clearance is a significant determinant of theophylline toxicity in newborns.[3-9] Consequently, in premature neonates whose glomerular filtration rate is lessened, theophylline clearance is likewise diminished, resulting in a much longer half-life, especially in an overdose situation. A summary of theophylline half-life and clearance according to age is in Table 2.

Due to its effectiveness in treating apnea of prematurity, reported cases of therapeutic misadventures with theophylline almost always involve premature neonates and usually require exogenous method of removal. In our patient who received 75 mg of aminophylline, the maximum expected drug level can be calculated using the following formula:

$$\begin{aligned} C_{max} &= C_{min} + (SFDose)/Vd \\ &= 0+0.8x1.0x75/(0.63x1.55) \\ &= 61.44 \text{ mg/L} \end{aligned}$$

whereas Vd for preterm infants is 0.63 L/kg.

The level taken post-exchange transfusion is 41.23 and 34.34 mg/L at 26 hours later, representing a decrease of 32%. The elimination constant of the drug can be calculated using the following formula:

$$\begin{aligned} K_e &= (InC2-InC1)/ T \\ &= (In5.22-In34.34)/89.5 \\ &= -0.021 \text{ hr} \end{aligned}$$

and the plasma half-life is

$$t_{1/2} = 0.693/Ke = 0.693/0.021 = 33 \text{ hours.}$$

TABLE 3. Theophylline clearance by exogenous pathways.[2]

Clinical Situation	Clearance	Half-life (hr)
Multiple-dose activated charcoal[†]	167 mL/min	3.3
Exchange transfusion	---	6-28(8)
Hemoperfusion	200 mL/min	2.0
Hemodialysis	125 mL/min	4.7
Peritoneal dialysis	9.5 mL/min	31

Thus, the estimated half-life of the drug post exchange transfusion is 33 hours while the reported half-lives vary between 28-53.3 hours.[8,10] The half-life of theophylline does not change from pre- to post-exchange transfusion. Other methods of enhancing elimination are substantially more efficient. Gitomer et al. reports a care of theophylline overdose in a 1,220-gram neonate treated with hemodialysis and achieved a half-life of 0.7 hours. When exchange transfusion is performed, the half-life during exchange transfusion, is reported to be 6.6 hours,[11] while that for multi-dose activated charcoal is 3.3 hours. As favorable as the latter treatment seems, the logistic of using charcoal orally in a premature neonate posses a valid concern for the risk of necrotizing enterocolitis.

CONCLUSION

After reviewing the kinetics of theophylline in premature infants, it is apparent that the ideal management of inadvertent overdoses should be the enhanced elimination of the drug through hemodialysis or hemofiltration. However, most communities and even some tertiary referral hospitals in Thailand lack equipments for both procedures as well as the expertise to carry out the tasks. Our case has demonstrated that prompt exchange transfusion together with good supportive care and monitoring can improve the outcome of theophylline poisoning in this high-risk population.

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บทคัดย่อ

การรักษาภาวะพิษจากยา theophylline ในทารกเกิดก่อนกำหนด

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วัตถุประสงค์: ในปัจจุบันยา aminophylline เป็นยาที่ใช้กันมากในกลุ่มผู้ป่วยทารกเกิดก่อนกำหนด ซึ่งทำให้เกิดความเสี่ยงเรื่องการคำนวน dose ยาผิดพลาด เมื่อให้แล้วทำให้เกิดภาวะพิษเฉียบพลัน นอกจากนี้แล้วเภสัชจลศาสตร์ของการกำจัดยา aminophylline และ theophylline ซึ่งเป็นรูปแบบยารับประทานยังมีความแตกต่างจากวิธีโดยทั่วไป กล่าวคือ จะขึ้นอยู่กับ renal clearance แทนที่จะผ่านทางตับ เช่นในผู้ใหญ่ ทั้งหมดนี้ทำให้การรักษาภาวะ overdose มีความซับซ้อน และทำให้การใช้วิธี enhance elimination เช่น exchange transfusion เพื่อช่วยกำจัดยาออกจากร่างกาย มีบทบาทในการรักษาภาวะพิษในทารกแรกเกิด

วิธีการศึกษา: ผู้ป่วยเด็กหญิงไทยอายุ 1 วัน เป็นทารกเกิดก่อนกำหนดอายุครรภ์ 30+5 สัปดาห์ น้ำหนักแรกคลอด 1,550 กรัม ได้รับยา aminophylline เพื่อรักษาภาวะ apnea of prematurity โดยได้ยาไป 75 มิลลิกรัม หลังได้ยาเริ่มมีอาการหัวใจเต้นเร็ว 190-230 ครั้ง/นาที อาเจียน ร้องกวน ระดับยา theophylline ในเลือดเป็น 30.77 mg/L ผู้ป่วยได้รับการรักษาด้วยวิธี blood exchange transfusion หลังทำทารกไม่มีข้อแทรกซ้อน อัตราเต้นของหัวใจลดลง (150-180 ครั้ง/นาที) ระดับยาในเลือดหลัง exchange transfusion ลดลงจากค่าคำนวณระดับยาสูงสุด 32% และคำนวณค่าครึ่งชีวิตของยา aminophylline ในผู้ป่วยรายนี้ได้เท่ากับ 33 ชั่วโมง ผู้ป่วยรายนี้สามารถกลับบ้านได้ที่อายุ 30 วัน โดยไม่มีข้อแทรกซ้อน

สรุป: Exchange transfusion มีประสิทธิภาพในการรักษาภาวะพิษเฉียบพลันในผู้ป่วยทารกเกิดก่อนกำหนด