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PHARMACOTHERAPY OF NEONATAL APNEA

R.H. Merchant
A.J. Irani

An apneic spell is defined as cessation of respiration for 20 seconds or longer, with or without decrease in heart rate; it also includes spells of lesser duration if associated with bradycardia or cyanosis. Apnea may be secondary to disorders of various organ systems in preterms or fullterm infants or primary "Apnea of prematurity". The latter is not associated with any other pathologic condition and characteristically develops within 3-5 days of life, in 25% preterms weighing ≤1800 g or born before 34 weeks gestation(1).

Besides treating the primary cause, where one exists, treatment of apneic spells comprises the following: tactile stimulation, proprioceptor stimulation by placing infant on an oscillating waterbed, maintenance of ambient temperature in lower neutral thermal zone, nasal continuous positive airway pressure of 2-4 cm water, use of respirogenic drugs and finally, mechanical ventilation where all other interventions fail. This review focuses on the pharmacotherapy of neonatal apnea.

Drugs that have been widely used in the treatment of neonatal apnea are the methylxanthines (theophylline and caffeine) and doxapram.

1. Theophylline

First used successfully by Kuzembo and Paala(2) in 1973, is currently the drug of choice in the treatment and prevention of neonatal apnea. It crosses the blood brain barrier and exerts its action centrally by stimulation of brain stem respiratory centre, and also increases the sensitivity of this centre to carbon dioxide. It antagonizes narcotic induced respiratory depression, improves diaphragmatic contractility rendering it less susceptible to fatigue, and hence regularizes the breathing pattern. Theophylline increases cardiac output and vital capacity thereby preventing recurrence of apnea, by eliminating hypoxia which is a primary factor in its occurrence.

From the B.J. Wadia Hospital for Children Parel, Bombay 400 012 and Nanavati Hospital, Vile Parle (W), Bombay 400 056.

Reprint requests: Dr. R.H. Merchant, Division of Neonatology, B.J. Wadia Hospital for Children, Parel, Bombay 400 012.

By improving blood glucose homeostasis and adrenergic effects it potentiates ventilation. At the cellular level it acts by inhibiting the enzyme phosphodiesterase thereby raising levels of cAMP. It also alters calcium ion flow into cytoplasmic matrix, has an antagonistic effect on prostaglandin, stimulates endogenous catecholamine release, inhibits cGMP and exerts beta-agonistic activity(3,4)

Pharmacokinetics: Given orally theophylline is almost completely absorbed, food slows down the rate of absorption but does not reduce the percentage absorbed. With elixirs peak plasma levels are reached in 15 minutes. Rectal absorption is unreliable. The plasma half life is 30 hours in preterms(5) in children it is 3½ hours and in adults 6 hours. Factors that reduce the half life include phenobarbitone and phenytoin, while those that increase its half life include CCF, liver diseases, and drugs such as erythromycin, cimetidine and propranolol. In neonates 30-40% of circulating theophylline is bound to plasma proteins, and is metabolized in the liver chiefly to caffeine(30%), small amounts of 1,3 dimethyluric acid are also formed and the balance excreted unchanged by the kidneys. Theophylline crosses the placenta and is excreted in breast milk.

Dose and Route of Administration: Theophylline is given orally or intravenously. Rectal route is not preferred as absorption is unreliable, irritant proctitis may occur, and incidence of nausea and vomiting is the same as with oral route(6). Intramuscular route is not employed as it causes severe pain lasting several hours. The dose is calculated so as to achieve a therapeutic blood levels of 6-12 μg/ml, though responses have been observed with lower levels(7).

In view of its long half life a loading intravenous dose of 5-7 mg/kg is required if therapeutic levels are to be reached quickly(1). The maintenance dose ranges from 2-4 mg/kg/day(8) although dosages as high as 6-8 mg/kg/day have been recommended by some authors(1). The final maintenance dose is guided by serum theophyline concentration, obtained after the steady state is reached. The oral dose in neonates is 6 mg/kg (loading) followed by 4 mg/kg/day (maintenance). The dose is lower in neonates because of slower elimination, higher mean apparent volume of distribution, and longer half life of the drug.

Therapeutic Blood Level Monitoring: On account of the narrow division between therapeutic and toxic doses and the significant variability in elimination kinetics in different patients, blood level monitoring assumes importance(4). Various micro-analytical techniques have been adopted for this purpose and they exhibit a range of sensitivity and specificity. Commonly employed techniques which include the immunoassays and chromatography require only small sample volumes (50 μl) and have a precision of 5-10%. The higher hardware cost of chromatography may be offset by the advantage to analyse other drugs. Immunoassays may be favoured for their ease of operation and the ability to use the technique on existing autoanalyser equipment within a clinical chemistry laboratory(4). Presently fluorescence polarization immunoassay (FPIA) and high performance liquid chromatography (HPLC), both highly sensitive techniques, appear to be the most popular methods in use.

In many centres in India facilities for drug level monitoring may not be available. In such cases the dose should be titrated to achieve maximum reduction in apnea without significant side effects.

Adverse Effects: There are uncommon below a plasma level of 10 μg/ml. The documented side effects include; (*a*) *Gastrointestinal*–gastric irritation, vomiting and hematemesis which are seen even with parenteral route of administration. Proctitis may follow repeated use of aminophyline suppositories. There does not appear to be any association between necrotising enterocolitis(9) and the use of theophylline, contrary to earlier reports; (*b*) *Cardiovascular*–tachycardia, arrythmias, and hypotension may occur specially in hypoxic patients with rapid intravenous boluses of the drug; (*c*) *CNS*–restlessness, irritability, tremors and convulsions. The latter rarely occurs at plasma levels ≤25μg/ml, however, these may occasionally be severe and fatal; (*d*) *Metabolic*–hyperglycemia, glycosuria, ketonuria, hypokalemia, and diuresis leading to dehydration may occur with high doses. Despite this long list of side effects, when used within the therapeutic range, the drug is very safe.

Discontinuing Medication: When apnea has resolved and if the infant weighs ≥1800 g and/or is 35-36 weeks post-conceptional age, the drug may be stopped and ideally a pneumogram obtained 4 days later. If this is normal the infant can be sent home without medication or monitor. If it is not possible to obtain a pneumogram, as in most set ups in our country, one should observe the neonate for recurrence of apnea over a period of 3-4 days after discontinuing treatment.

Table I summarises the theophylline content of various salts and forms they are marketed in.

2. Caffeine Citrate

As a centrally acting respirogenic agent, it is equally if not more effective than theophylline(10,11). It has less peripheral effects than theophylline. Caffeine is available in some countries as tablets of 100 mg and as injection containing caffeine sodium benzoate 125 mg/ml. This latter compound is not recommended in neonates because of risk of hyperbilirubinemia. Commercial preparations of caffeine citrate are not available, but the compound can be obtained from drug companies and prepared by a pharmacy as an aqueous solution providing 20 mg/ml for intravenous or oral use. Oral route gives similar plasma concentration as that achieved by intravenous rate. Being very acidic, caffeine citrate should not be given intramuscularly. The recommended loading dose is 10 mg/kg of base which gives a plasma

TABLE I–*Theophylline Content of Various Salts and Forms they are Marketed*

	Theophylline salt	Theophylline content%	Available formulation
1.	Aminophylline	85	IV/IM injection, tablets, elixirs
2.	Choline theophyllinate	64	Tablet, elixir
3.	Theophylline ethanoate of piperazine	56	Syrup
4.	Theophylline sodium glycinate	50	Elixir

concentration of 8-14 μg/ml which is the effective therapeutic range(12). The maintenance dose is 2.5-5 mg/kg/day of the base given as a single daily dose. The half life of caffeine decreases from 100 hours in neonates to 6 hours by about 60 weeks post-conceptional age. Caffeine has a large margin of safety, whereas the therapeutic level is ≤20 μg/ml, toxicity is seen with levels >50 μg/ml.

3. Doxapram

This is a potent respiratory stimulant with a wider margin of safety than other analeptic agents. It is effective in treating refractory apnea in neonates already receiving therapeutic doses of theophylline(13).

Mechanism of action: In low doses it selectively stimulates respiration by acting on carotid chemoreceptors, while in larger doses it stimulates the medullary respiratory neurons. Since methylxanthines act primarily by central stimulation, some cases wherein there is excessive depression of respiratory centres, may require the peripheral action of Doxapram to arouse respiration. This may explain the effectiveness of doxapram in cases where methylxanthines fail.

Pharmacokinetics: When given intravenously, doxapram has a rapid onset of action, within minutes, and a short duration of residual effect upon discontinuation–not more than 5-10 minutes. This may be because a large fraction of the drug is initially delivered to the brain followed by redistribution to other tissues. Doxapram has a serum half life of 5-13 hours. It is excreted by the kidney after rapid metabolism.

Preparation: Doxapram is available for injection in 5 ml and 20 ml vials containing 20 mg/dl, and is marketed under the trade name "Dopram".

Dose and Route of Administration (14-16)*:* It is administered as a continuous intravenous infusion in 5% dextrose or dextrose saline, and is incompatible with solutions containing aminophylline or furosemide. An initial loading dose of 1-1.5 mg/kg is followed by a maintenance dose of 0.5-2.5 mg/kg/h titrated to the lowest rate at which apnea is controlled. The desired therapeutic level is less than 5 μg/ml.

Adverse Effects: Unlike theophylline, doxapram has a wide margin of safety. Side effects are usually mild and reversible and include (*a*) *CNS*–jitteriness, irritability, and seizures. Doxapram induced seizures, which necessitate drug withdrawal, can be controlled with diazepam; (*b*) *Gastrointestinal*–increased gastric residual, vomiting, and abdominal distension; (*c*) *Cardiovascular*–hypotension and cardiac arrhythmias; (*d*) *Miscellaneous*–hyperpyrexia, hyperglycemia, glycosuria and disordered liver functions have all been noted.

Caution: Doxapram must be used with caution in infants with seizures, and during the first few days of life when hypertensive episodes may increase risk of intraventricular hemorrhage. The currently available preparation contains benzyl alcohol which may accumulate to toxic levels.

Conclusions: Doxapram should be considered in neonates with apnea refractory methylxanthine therapy or CPAP, prior to intubation and mechanical ventilation. It may be noted that theophylline has also been shown to be equally effective for apnea refractory to doxapram therapy(17).

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EMERGENCY TIPS

J.S. Surpure

Cardiac Contusion

Cardiac contusion secondary to blunt thoracic trauma is an important entity that has been recently characterized in the adult patient population. The frequency of cardiac contusion in pediatric patients who sustained significant blunt thoracic trauma has not been reported previously. Ildstad *et al.*(1) retrospectively studied 7 patients ranging in age from 2 to 18 years who had rib fractures or pulmonary contusion.

Reprint requests: Dr. J.S. Surpure, Associate Professor, Department of Pediatrics, Emergency Medicine and Training Centre, Oklahoma Medical Centre, 800 Northeast 13th Street, 1700 Jessie James, Oklahoma City, OK 73104, U.S.A.