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Risks and Benefits of Therapies for Apnoea in Premature Infants

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Contents

Abstract

Apnoea in infants can result from a wide range of causes, and requires thorough evaluation before deciding on appropriate treatment. Continuous monitoring of premature infants with apnoea is mandatory in order to define the pathophysiology and type of apnoea; selection of treatment involves careful assessment of aetiology, as well as efficacy and tolerability in each individual case. The objective of treatment is to prevent the deleterious consequences of apnoeas that last >20 seconds and/or are associated with bradycardia, cyanosis or pallor, and occur more often than once an hour over a 12-hour period.

Apnoea management involves both pharmacological and nonpharmacological treatment. We suggest methylxanthines as first-line therapy for idiopathic apnoeas; evidence suggests that caffeine is better tolerated and as efficacious as theophylline (since it is particularly efficacious against the 'central' component of idiopathic apnoea of prematurity). If treatment fails, additional measures such as doxapram may be appropriate when hypoventilation is present, or nasal continuous positive airway pressure when upper airway instability or obstructive apnoeas are predominant. Apnoea prophylaxis is an additional reason to advocate prenatal maturation with betamethasone. Weaning from treatment is attempted 4 to 5 days after complete resolution of apnoea, beginning with the last treatment introduced. Monitoring should be maintained for 4 to 5 days to detect any relapse of recurrent and severe apnoeas, which would lead to the resumption of the most recently withdrawn treatment.

1. Introduction

Apnoea is defined as a transient cessation of breathing that can also be associated with bradycardia and desaturation.[1] Although apnoeic episodes are worrisome to the physician, their long term consequences are yet not clear and they have a wide range of possible causes.[2-4] Thus, careful evaluation of the type of apnoea, its aetiology, its physiopathology and its tolerance is mandatory before deciding on a treatment, as inappropriate treatments are potentially harmful.[5]

The instability of respiratory and cardiac rhythms is a characteristic of the premature infant.[6] It reflects an immaturity of the respiratory drive and unbalanced autonomic and parasympathetic tones.[7,8] This leads to an inverse relationship between postconceptional age (i.e. maturation) and apnoea incidence and severity. Since survival of extremely premature infants has markedly improved within the past decade, apnoea of prematurity is one of the most common problems dealt with in a neonatal unit. Management of premature infants with apnoea involves pharmacological and nonpharmacological therapies. All these therapies have beneficial effects when used appropriately in the treatment of apnoea.

In order to propose an appropriate management for apnoea of prematurity, we performed a review of available publications regarding the risks associated with apnoea, and the risk-benefit ratio of the current treatments. The database of PUBMED® (National Library of Medicine), REPROTOX® and TERIS® were screened in order to collect prospective studies, published recommendations, case reports of treatment adverse effects and physiological studies dealing with apnoea of prematurity. Editorials, general reviews, letters and publications not reporting original data were not included. 276 papers were analysed and 168 synthesised in this review.

1.1 What is Apnoea of Prematurity?

Idiopathic apnoea of the premature infant may be considered as a developmental state that will resolve over time (with maturation); however, it is potentially harmful because of its acute consequences on gas exchange and haemodynamic disturbances.[9-14]

Apnoeas, occasionally accompanied by hypoventilation and upper airway instability in very premature infants,[15] occur mainly during active sleep, which represents the primary behavioural state in newborn infants.[6,7] The arousal threshold appears to be depressed compared with that of quiet sleep.[1] Prolonged (>20 seconds) and recurrent apnoeas may compromise oxygenation, potentially facilitating the occurrence or aggravation of brain lesions, especially when associated with bradycardia and desaturation.[11-14]

The relationship between apnoea of prematurity, bradycardia and desaturation is complex.[4,16] Most often, apnoea is the initiating phenomenon causing a desaturation, which leads to a bradycardia.[9] In the absence of airflow measurement, obstructive or mixed apnoea is identified as a bradycardic episode with desaturation.[17] Central, mixed and obstructive apnoeas appear to be part of a continuum rather than separate entities, since airway closure may occur in any apnoea lasting more than 20 seconds[18] and diaphragmatic action is not mandatory to occlude the airways.[17] This may explain why some infants with central apnoea who do not respond to central stimulants can respond to continuous positive airway pressure (CPAP), or why some infants with mixed apnoea can respond to central stimulants.[19,20] In addition, bradycardia as a primary event followed by desaturation may cause respiratory drive depression leading to apnoea.[8]

In very premature infants, failure to maintain appropriate lung volume may cause recurrent apnoeic spells with desaturation and intrapulmonary shunting. This shunting aggravates further hypoventilation. Thus, vigorous treatment is required to prevent acute respiratory failure.[21]

Not all apnoeas of the premature infant are idiopathic apnoea of prematurity. They may be secondary apnoeas and therefore require appropriate aetiological management.

1.2 Indications for Apnoea Treatment

All secondary apnoeas require vigorous appro-

priate treatment, and various conditions must be considered. Bacterial sepsis must be ruled out, particularly when apnoea occurs within the first hours of life in relation to materno-fetal infection, or after the second week of life (usually secondary to nosocomial infection).[1,22] Apnoea may also be associated with viral infections, which may reinforce reflex apnoea.[23]

Secondary apnoeas may also be attributable to patent ductus arteriosus,[24,25] gastro-oesophageal reflux,[26,27] seizures, severe anaemia or hypovolaemia,[28,29] maternal or neonatal medication or intoxication, acute or severe chronic pain,[30] bowel distension,[31] upper airway congenital malformation,[32] nasal obstruction or several metabolic disorders such as hypothyroidism,[33,34] hypoglycaemia[35] or hypocalcaemia.[36] Hypo- or hyperthermia are frequently associated with apnoea.[1] However, even when an infant's temperature appears to be normal when measured peripherally, an elevated central temperature or cold stimulation to the trigeminal facial area can induce apnoea.[22,37]

All these aetiologies have been described in association with apnoea, but a direct causal effect has rarely been demonstrated. It is noteworthy that immaturity enhances the incidence and severity of the apnoea associated with any pathological condition.[6]

Idiopathic apnoeas do not appear to directly cause severe intracranial abnormalities or severe neurodevelopmental disabilities.[38] However, they may be associated with more subtle neurodevelopmental, cognitive, sleep disturbances later in childhood,[3] or be a marker for pathological events and subsequent neurodevelopmental disorders.[2] Moreover, when associated with bradycardia, prolonged apnoeas lead to significant haemodynamic disturbances and hypoxia. Thus, it may seem wise to follow the recommendations of the American Academy of Paediatrics[39] and consider treatment for prolonged apnoea,[11] defined as a cessation of breathing for at least 20 seconds or as a briefer episode of apnoea associated with bradycardia, cyanosis or pallor.[11] However, small numbers of well tolerated apnoeas should not automatically be considered sinister, especially when there is no associated bradycardia. After excluding specific aetiologies, continuous monitoring of respiratory and electrocardiogram waveforms associated with pulse oximetry is probably the most appropriate management.[40]

As these apnoeas are a normal manifestation of immaturity, the objective of treatment is not to cure them but to prevent potential deleterious consequences. Thus, indications for treatment should also include whether the apnoeic spells are recurrent: only apnoeas that are ≥20 seconds in duration and/or associated with bradycardia, cyanosis or pallor, and occur more often than once per hour over a 12 hour period.

2. Pharmacological Treatment of Apnoea

Respiratory stimulants used in the treatment of apnoeas are mainly methylxanthines (caffeine and theophylline) and doxapram, as shown in table I.

2.1. Methylxanthines

Theophylline (1-3-dimethylxanthine) and caffeine (1-3-7-trimethylxanthine) are central nervous system stimulants endowed with respirogenic properties. Vogl[41] described the first therapeutic use of aminophylline in 1927 for the treatment of Cheyne-Stokes respiration but it was not until much later that methylxanthines were introduced into the management of apnoea in the premature infant.[42] Both theophylline and caffeine increase chemoreceptor sensitivity to CO_2 and resultant transmission of neural impulses, improve respiratory muscle contractility and metabolic homeostasis, and enhance the response to catecholamines. The xanthines are antagonists of endogenous adenosine, which is a central respiratory-depressant and, in contrast, is also a peripheral respiratory-stimulant. They attenuate this respiratory stimulation.[43] The major mechanism of action of the methylxanthines on the control of breathing, contributing to their 'antiapnoeic' effect, seems to be an increase in respiratory centre output that leads to an increase in ven-

Table I. Characteristics of the drugs most usually prescribed for treatment of apnoea in infants

	Theophylline	Caffeine	Doxapram
Able to be used in combination with other therapies?	Yes	Yes	Yes
Dosages in neonates	Established (oral, IV)	Established (oral, IV)	Dosage guidelines not yet established
Route of administration	Oral + IV	Oral + IV	IV
Tolerability	Good	Good	To be determined
Correlation between dose and plasma concentration	Weak	Good	Weak
Commercially available preparation suitable for infants?	Not available	Not available	Not available
Specific indication	Apnoea	Apnoea	Functional hypoventilation in VLBW infants
Current use	Wide	Wide	Restricted

IV = intravenous; **VLBW** = very low birthweight.

tilation. This has been shown in newborn animals and in premature infants treated with caffeine.[44]

Several open studies confirmed Kuzemko and Paala's initial report. [42] In 8 low birth weight infants given 4 mg/kg of 10 % alcohol elixir of theophylline by nasogastric tube every 6 hours for 1 week; severe apnoeic episodes recorded by impedance pneumogram were completely controlled and mild episodes of 10 to 19 seconds were significantly ($p=.002$) decreased from a mean of 28.5 ± 20.4 in 13 hours to 5.6 ± 4.3.[45] In 12 severely apnoeic premature babies requiring assisted ventilation (Ambu-bag resuscitation) from 2 to 10 times in 24 hours, oral theophylline at a dose of 4 mg/kg every 6 h induced a significant ($p < 0.005$) reduction in the severe apnoeic spells 6 hours after the initial dose of the drug.[46] 6 of 13 infants given from 1.7 to 6.4 mg/kg aminophylline by the rectal route every 6 hours became free of apnoeas (identified by an impedance apnoea-monitor) 72 hours after the onset of treatment. The response in each 8-hour interval when compared to the pretreatment period was significant ($p < 0.01$) for all intervals except the first.[47] The use of 4 to 8 mg/kg theophylline per rectal route every 12 h, for a short or long course (2 or 5 days) in 10 premature infants monitored by thoracic impedance and transcutaneous oxygen-electrode resulted in the significant reduction ($p < 0.01$) of apnoeic spells. Similarly, significant ($p < 0.01$) decreases were observed in the total duration of hypoxaemia, but also of hyperoxaemia, which was reduced by more than 50 % in 9 of the 10 babies. This unexpected but important effect of theophylline must be enlightened, because hyperoxaemia is the reverse danger of oxygenotherapy and may be responsible for retrolental fibroplasia and other sequelae of oxygen toxicity. This reduction may be due in part to fewer interventions for giving oxygen for apnoeic spells.[48] A blinded trial showed that the rate per hour of apnoea attacks fell below the threshold of 0.33 (considered as a positive response) in 8 infants out of 10 treated with theophylline versus only 2 infants out of 10 given a placebo.[49]

Some investigators initially preferred caffeine to theophylline for the treatment of apnoea.[50] They showed in a nonblinded, noncontrolled study that caffeine (5 to 10 mg/kg once to 3 times daily for 6.0 ± 1.9 days) dramatically decreased the mean daily number of apnoeas from 13.6 ± 2.5 to 2.1 ± 0.6 ($p < 0.001$) in 18 premature infants. A complete cessation of apnoea was noted in 6 of the 18 infants, and a significant decrease (at least 50 %) was observed in 17 of the 18 infants.[51]. Moreover, caffeine reduced the need for mechanical ventilation: in a controlled, nonblinded study, 21 caffeine treated infants were compared to 21 matched controls. Only 3 treated infants required intermittent positive pressure ventilation against 14 controls ($p < .001$), the duration of mechanical ventilation being 0.9 ± 2.5 days for the treated group versus 7.5 ± 13.7 days for the controls ($p < 0.05$).[52] In 8 infants, the sum of cardio-respiratory abnormalities per 100 min (ap-

noea ≥ 15 seconds, episodes of bradycardia <80 beats/min, apnoea plus bradycardia <100 beats/min) significantly decreased ($p < 0.01$) from 0.7 ± 0.3 before treatment to 0.4 ± 0.2 after 3 days of treatment.[53] A nonblinded trial (44 participants) showed significant reductions ($p < 0.02$ and $p < 0.01$) in the number of apnoeas treated with caffeine or theophylline between day 0 and day 1.[54]

The percentage of full and partial success with all methylxanthines (success defined either as a significant reduction of apnoeic spells, or complete cessation of apnoeas, or a >50% reduction in the number of apnoeas) ranges from 33 to 100% across these trials.

The accumulated evidence in favour of methylxanthine efficacy, and the fact that infant apnoeas are a severe pathology, previously deprived of pharmacological treatment and managed solely with assisted ventilation, explains why no extensive placebo-controlled trial has been undertaken after these initial publications. However, such a trial would be essential to definitively confirm the efficacy of methylxanthines in relation to improving long term outcome.

Therapeutic drug plasma concentrations of 8 to 20 mg/L have been defined for caffeine,[55] but a range has not been defined with confidence for theophylline partly because of the contribution from the metabolite caffeine. In our daily experience, we measure the cumulative methylxantine plasma concentration (caffeine plus theophylline) and aim to maintain it under 20 mg/L.

Studies have also assessed the comparative efficacy and tolerability of caffeine and theophylline. Two randomised double-blind trials did not find any marked difference between the two agents in terms of their abilities to reduce the incidence of apnoea and bradycardia.[53,56] In contrast, as early as the first day of treatment, we observed a significant ($p < 0.05$) acceleration in heart rate in 10 theophylline-treated infants (4 mg/kg/day) monitored by hard copy recordings (Hewlett Packard Cardiorespirograph).[53] The heart rate was significantly higher in the theophylline group than in the caffeine group ($p < .01$ to .001 during the 7 days of the trial). Moreover, theophylline appeared less well tolerated by the gastrointestinal tract: oral feeding had to be stopped in 4 infants given theophylline and in 2 of these infants, signs of necrotising enterocolitis subsequently developed; no significant gastrointestinal side effects were observed in the caffeine group. The therapeutic to toxic ratio is narrow for theophylline. In contrast, caffeine plasma concentrations are more strongly correlated to dosage[57] with less variation.[53] Thus this methylxanthine is often preferred to theophylline.

Rational dose guidelines for methylxanthines were established on the pharmacokinetic data.[50] Methylxanthine half-lives are much longer in neonates than in nonsmoking adults: about 30 hours for theophylline and 60 to 100 hours for caffeine *vs* 5 and 6 hours, respectively. Caffeine clearance and volume of distribution have been shown to be significantly influenced by postnatal age, current body weight and a gestational age >28 weeks.[57] The current theophylline loading dosage is 6 mg/kg, then 2 mg/kg twice daily as maintenance therapy. Plasma concentrations with this regimen are about 6 to 9 mg/L.[53] With a higher dosage regimen (7.5 and 9 mg/kg as loading and maintenance doses, respectively) the plasma concentrations range from 13 to 20 mg/L.[54] Caffeine base loading dose is 10 to 12.5 mg/kg and the maintenance dose of 2.5 to 3 mg/kg/24h, once daily.[50] Plasma concentrations are about 6 to 20 mg/L. Following these guidelines, complete cessation of apnoea is obtained in 30% of the cases within the 2 or 3 first days of administration.[51] In most of the remaining cases, the treated infants experience at least a 50% decrease in incidence of apnoeas, they do not require assisted ventilation and stop spontaneously having apnoeas.

Higher doses of caffeine have been tested in 16 infants:[54] 25 mg/kg as a loading dose and 6 mg/kg over 24 hours as maintenance therapy. These high doses were compared to conventional doses given to 14 infants. They achieved a faster response (within 8 h) than the conventional doses.[54] However, both normal and high dose regimens produced significant reductions in the mean number of apnoeic at-

tacks within 24 hours: from 22.8 to 15.9 ($p < 0.05$ and $p < 0.02$) and from 22.7 to 10.0 ($p < 0.001$), respectively. Both regimens were well tolerated by the 30 very preterm infants. Apnoeas were eliminated completely by 48h only in some infants of the high dose group. Mean plasma concentrations of caffeine achieved at day 5 were 15 and 30 mg/L for standard and high doses, respectively.

More recently, Stephenson[58] published his personal practice. He used high doses of caffeine, i.e. 25 mg/kg of caffeine base as loading dose and 6 mg/kg/24h as maintenance, without any apparent adverse effects, but the achieved plasma concentrations were not given.

A wide range of adverse effects has been described with methylxanthines, from mild effects to acute toxicities. The adverse reactions are mainly exaggerations of the pharmacological actions such as tachycardia, [59,60] high arterial pressure,[61] increased gastric aspirations [62] or increased duration of acid gastro-oesophageal reflux[63] and jitteriness[50]. The role of methylxanthines in the occurrence of necrotising enterocolitis remains controversial, as this pathology is possibly related to other circumstances linked to both prematurity and apnoea, such as hypoxia and intestinal immaturity.[64]

Dramatic adverse effects resulting from overdoses of both drugs have also been published. A full-term resuscitated infant became extremely jittery and exhibited tachypnoea 6 hours after administration of 100 mg/kg caffeine. Plasma concentrations were 55 and 52 mg/L at 24 and 36 hours of age. Later he was asymptomatic with a plasma concentration of 28 mg/L.[65] Banner and Czajka[66] described 4 cases of acute caffeine overdose. Newborn babies were given single caffeine doses of 36 to 136 mg/kg and subsequently developed tachypnoea, tremor, opisthotonos and tonic-clonic movements. Plasma concentrations of caffeine were 31.9 mg/L in 1 infant with moderate opisthotonic posturing, 13.7 and 26.1 mg/L in another infant with rigidity and clonic movements and 79.9 mg/L in a third infant with seizures. More recently, an extreme intoxication has been reported with an unknown dose of caffeine in a premature male neonate who developed tachycardia, compromised circulation, vomiting and seizures. The serum drug concentration was 346 mg/L. The baby survived without any sequelae at the age of 18 months.[67] Gorodischer[60] observed that plasma concentrations of caffeine above 100 mg/L were associated with tachycardia (200 to 260 beats per minute) and mild glycosuria. Aranda[55] observed that infants were only transiently jittery with plasma concentrations from 50 to 84 mg/L.

Reasons for these discrepancies are unclear, but they indicate the need to be very cautious with the use of methylxanthines. For caffeine, plasma concentrations above 40 mg/L should be avoided and concentrations should be kept within the optimal range for the control of apnoea.[50] For theophylline, plasma concentrations should be kept <20 mg/L, the threshold above which tachycardia will occur.[54] As theophylline is methylated into caffeine in significant amounts by the premature neonate,[59,68] it may be useful to monitor the cumulative methylxanthine (theophylline plus caffeine) concentrations during theophylline therapy. Drug concentration monitoring is mandatory as soon as therapeutic failure is suspected or when clinical signs of intolerance are observed.

For both methylxanthines, blood samples should be taken when the steady-state is reached for routine monitoring, just before the next dose in case of therapeutic failure and 2 to 4 hours after the previous dose when suspecting toxicity. Routine plasma concentration measurement should be made once a week during treatment with caffeine and 2 or 3 times a week with theophylline.

Potential long term adverse effects of methylxanthines have also been investigated. Clinicians have been concerned at the potential risk of cerebral damage and impairment of neuronal development with xanthine derivatives, since these drugs are known to raise cerebro-vascular resistance and contribute to a reduction in cerebral blood flow in animals and in adult humans.[69,70] Cerebral blood flow, measured by the Xe clearance technique, was significantly lower 2 hours after 5 mg/kg aminophylline than after 20 mg/kg caffeine citrate.[71] Using Doppler ultrasound, others showed that the same dose of

caffeine citrate did not induce any significant changes in cerebral blood flow velocity.[72,73]

Another potential cause of cerebral damage is related to the blocking of adenosine A1 and A2 receptors by theophylline and caffeine, as adenosine plays a role in cerebro-protection against hypoxic insult. [74] In our laboratory, it has been shown that blocking adenosine A1 receptors with theophylline can enhance cell injury induced by 8h hypoxia in cultured neurons.[75] However, a prospective follow-up of 21 infants treated with caffeine at conventional doses[51] for 6.0±1.9 days compared with matched controls indicated that caffeine had no apparent harmful effects 18 months to 3 years later.[52] In addition, no difference was found in psychomotor development or incidence of cicatricial retrolental fibroplasia. Although the sample size is too small to ensure detection of significant adverse effects, no severe neurological impairment has been reported so far with regard to any infant receiving methylxanthine treatment.

In summary, the use of methylxanthines is certainly beneficial for the treatment of apnoeas in the preterm infant. The adverse effects are known and can be prevented easily by a close clinical, blood test and pharmacological monitoring.

However, unintentional overdoses are still possible because of the absence of convenient commercial preparations that fit with the very small amounts of drug required to treat the low birthweight infants. This problem is often solved in a satisfactory way, for caffeine, by the hospital pharmacists who make solutions for oral or intravenous use containing 5 or 10mg caffeine base per ml.[5,54,58,60,76] An other possible source of confusion is the fact that 2 terminologies are quoted in the literature: caffeine base and caffeine citrate, with 10mg of caffeine base being equivalent to 20mg of caffeine citrate. A standardization should be done by using the term caffeine base only.

2.2. Doxapram

Doxapram (pyrrolidinone derivative) is a potent respiratory stimulant. In adults, it increases minute-ventilation by increasing respiratory frequency;[77] this usually results is a decrease in PCO_2[78,79] and an increase in PO_2[80]. The mechanism of action is poorly understood and seems to rely upon the dose. At a low dose, the site of action is peripheral at the level of the carotid bodies,[81] whereas at higher doses, the action is preponderantly mediated through the brain and the medulla system. The number of centres stimulated increases in parallel with the dosage.[82]

The major metabolite, ketodoxapram, exhibits the same ventilatory effects, but is less potent. [83] It appears to be better tolerated than doxapram by newborn lambs.[83] Using a cross over design, agitation and a significant ($p<0.01$) increase in blood pressure were observed in 12 newborn lambs when they were infused with doxapram and not when they were infused with ketodoxapram.[83] No information is available to date in humans.

Doxapram is an inducer of microsomal drug metabolising enzyme activity.[84] It increases the amount of cytochrome P450 and the activities of numerous drug N-demethylases.[85] However, no pharmacokinetic interactions between doxapram and theophylline has been observed.[86]

Doxapram has been reported to be effective in the treatment of respiratory depression of the neonate,[87,88] in recurrent apnoeas of prematurity[89] and in congenital central hypoventilation syndrome.[90] Its efficacy on apnoea has been evaluated in some nonblinded, noncomparative, noncontrolled small clinical trials. The apnoea attack rate decreased significantly ($p <0.01$) within 6 to 24 hours in 12 infants given 2 to 2.5 mg/kg/h for 1 day. The mean number of apnoeic episodes per hour decreased from 0.95 before treatment to 0.16 between 6 and 24 hours after starting infusion.[91] In 5 infants, apnoeas were completely abolished after 6 hours of therapy. Total disappearance of apnoeic episodes occurred in 9 of 12 patients given doxapram at the initial infusion rate of 1 to 1.5 mg/kg/h[92].

The efficacy of doxapram in reducing or eliminating apnoea incidence is dose-dependent. In a study of 18 infants experiencing apnoea monitored continuously by oxycardiorespiratographic recordings (and spirometric and occlusion studies re-

peated 24 or 48 hours after starting therapy), doxapram was given at an initial dose of 0.5 mg/kg/h by intravenous infusion. The dosage was increased by 0.5 mg/kg/h after each spirometry and occlusion study in case of nonresponse. 'Response' was defined as a reduction in apnoea frequency to 2 episodes or less in any 6-hour period. 'Nonresponse' was defined as continuation of apnoea at a frequency of 4 or more episodes in any 6-hour period. The treatment was successful in 47 and 89 % infants given 0.5 or 2.5 mg/kg/h, respectively.[93] A reduction of 48 and 75% in the mean frequency of apnoeas was observed in 8 infants given doxapram 0.25 mg/kg/h for 24 hours, then 1 mg/kg/h for a further 24 hours. The study was not blind nor randomised, all infants were investigated in the same way by the mean of cardiorespirography, spirometry and airway occlusion pressure.[79]

The combination of doxapram and theophylline seems to be more effective at decreasing the rate of apnoeas than doxapram alone at a dosage of 2.5 mg/kg/h.[49] Apnoea decreased significantly from 16.7 to 2.1 in 24 hours ($p < .001$) in the doxapram alone group ($n = 10$; 1.5 ± 0.7 mg/kg/h after an I.V. bolus of 2.5 mg/kg/h) and from 38.2 to 7.9 in 24 hours ($p < .001$) in the doxapram (same dosage) + theophylline group ($n = 6$; dosage not specified). In a blinded, randomised, controlled trial, doxapram given to 11 infants as a loading dose of 3 mg/kg followed by a continuous infusion of 1.5 mg/kg/h has been shown to reduce significantly the incidence of apnoea within 48 hours and to be more effective than a placebo given to 10 infants ($p < 0.01$). The baseline rate of episode of apnoea remained unchanged in the placebo group. The response to theophylline did not differ from the response to doxapram in 10 infants.[49] Another trial compared 14 infants treated with doxapram with 15 given placebo. Heart rate, respiration and blood pressure were continuously recorded during the 5 days of infusion plus 1 day following the end of the infusion. Following early weaning from assisted ventilation, infants experienced significantly ($p < 0.02$) fewer moderate apnoeas (defined as attacks longer than 10 seconds associated with bradycardia <80 beats per minute for more than 30 seconds) when they were treated with doxapram (0.5 mg/kg/h) than with a placebo.[94] In contrast, an infusion of doxapram (1 mg/kg/h) administered prior to extubation to very low birthweight infants during the first 3 weeks of life did not increase the likelihood of successful extubation versus a placebo infusion.[95]

The plasma concentrations of doxapram described as effective in the treatment of apnoea, range from 0.47 to 5 mg/L.[78,93,96,97] Ketodoxapram, although a respiratory stimulant itself, is usually not taken into account in assessing therapeutic concentrations.

Dosage schedules were initially extrapolated from adult data: 2.5 mg/kg/h by continuous intravenous infusion.[89,91,98-100] Plasma concentrations obtained in these conditions were about 5.8 ± 1.8 mg/L.[100] More recently, the tendency has been to give lower amounts of doxapram, 0.5 to 1.5 mg/kg/h, with or without a preceding 3 mg/kg loading dose,[49,95,96] which leads to mean plasma concentrations of 1.3 to 3.13 mg/L.[49,78,94] The correlation between dose and plasma concentrations is good,[92,93] but the interindividual variability is high.[101] Moreover, some authors[94,97] have noted a trend towards higher plasma concentrations of doxapram within the first week of life, and less variation in concentrations after 7 days.

Doxapram is rarely given by enteral route; if this is done, it should be given by nasogastric administration with the regular feeding, over 1 hour. The trials have used doxapram every 6, 8 or 12 hours with a large range of doses: 16 to 96 mg/kg/24h.[78,90,102-104] The enteral dose is usually calculated as the intravenous dose + 50%.[105] In such conditions, the switch from the intravenous to the enteral route leads to stable plasma concentrations within the therapeutic range.[102]

Much higher oral doses have been used (144 mg/kg/day in 2 cases) but have resulted in excessive plasma concentrations (14.6 mg/L on day 3).[106] The elimination half-life of doxapram is longer in premature infants than in adults: 6.6 to 9.9 h[93,96,100,105] versus 3.4 h in adults, respectively.[107] After oral or intravenous administration, doxapram is rapidly

oxidated into the active metabolite ketodoxapram. This metabolic transformation is already occurring in the human fetal liver at 10 to 16 weeks gestational age.[106]

Adverse effects have been observed with the use of doxapram in neonates. However, 1 of these may be attributable to the preservative (benzyl alcohol) present in the formulation marketed in the US and South Africa. Benzyl alcohol has been associated with a gasping-syndrome,[108] for daily doses of benzyl alcohol of 99 to 234 mg/kg, which is far greater than the concentrations associated with therapeutic dosages of doxapram. In any case, this risk led the manufacturer to emphasize that formulating injectable doxapram with benzyl alcohol was contraindicated for administration to newborns.[109]

In Canada and Europe, the preservative present in the commercially available formulation is chlorobutanol. Although the toxicity of chlorobutanol has not been evaluated in neonates, no adverse effect clearly linked to this agent has yet been reported.

Data about the risk of adverse effects resulting from doxapram administration to low birthweight infants are conflicting. The rate of adverse effects varies from 16 to 75% accross studies;[78,92,94,97] this is because definitions of adverse effects and the methodology of recording these differed across studies. In addition, some of the following adverse effects are very frequent, mild and sometimes not recorded as adverse effects by the investigators: increased gastric residue, excessive salivation and mild irritability.

Other effects, observed in controlled trials and occurring at the same rate in the placebo- and the doxapram-treated groups, were considered to be prematurity-related complications (necrotising enterocolitis, intraventricular haemorrhage and periventricular leukomalacia) and were not taken into account in assessing tolerability.[94] However, they may be recorded as adverse effects in noncontrolled trials, even though the absence of control patients makes it impossible to associate the effect with the drug rather than the prematurity of the infants.

Out of some 30 papers published in the past 2 decades on the use of doxapram in neonates, half of them include data on adverse effects. Some authors have noted a link between high doses and high rates of adverse effects.[97] The most frequently recorded adverse effects are digestive troubles: increased gastric residue, vomiting, abdominal distension, bleeding in the stool and necrotising enterocolitis.[78,89,90,92,97,100,104,105,110] In most cases,[78,104,106] these digestive troubles, including duodenal ulceration and necrotising enterocolitis, occurred when the drug was administered by an intravenous infusion without any prior enteral administration, suggesting that it may be a general intolerance of that administration route.

All the adverse effects listed above are exceptionally severe and life threatening. Their frequency cannot be assessed on the basis of the published data, the given information being often vague and the numbers of patients too small. We are completing a prospective study on this topic, which suggests that the mild digestive troubles are very often observed during doxapram administration, not always linked to an intolerance and usually compatible with the continuation of the treatment.

The following adverse CNS effects were noted during doxapram treatment in some studies: alarming state of jitteriness, seizures, irritability and increase of time spent awake.[91,99,104] The information given by the authors does not indicate the incidence of these adverse effects.

Another undesirable effect observed in some studies was the effect on arterial blood pressure: an increase in mean arterial blood pressure[111] and hypertension sometimes experienced by patients receiving high doses.[93] Three cases of atrioventricular heart block have been associated with doxapram administration in infants.[103] In the first case, the patient received an infusion of 1.47 mg/kg/h of doxapram for 36 hours, in the second case, doxapram was given orally at the dose of 15 mg/kg every 6 hours and in the third case, an infusion of 3.08 mg/kg/h of doxapram was associated with oral aminophylline (5 mg/kg/d) for 6 days. However, it is possible that other factors such as the preservative (benzyl alcohol) and associated medications, among them cisapride, may have been in-

volved. Finally, a possible effect of doxapram on bone maturation has been raised by Tay-Uybocco,[78] who observed early teeth eruption in 4 premature infants after a few weeks of treatment at the doses of 1 to 2.5 mg/kg/h and with drug plasma concentrations of 0.85 to 2.04 mg/L.

An accurate relationship between plasma concentrations of doxapram and toxicity has not been demonstrated. A few mild and reversible adverse effects were noted in 16 infants with doxapram plasma concentrations as low as 0.39 mg/L.[78] In 30 infants treated with doxapram by continuous infusion (0.5 to 2.5 mg/kg/h) or by the enteral route (7.5 mg/kg, 4 times/d) for a mean duration of therapy of 15.5 days, the mean plasma concentration of doxapram at which the adverse effects occurred was 1.0 mg/L, the lowest concentration being 0.47 mg/L.[97] In our experience, we observed severe adverse effects in 5 out of 297 infants treated with doxapram. The plasma concentrations related to these severe adverse effects ranged from 7.1 to 14.0 mg/L for doxapram and from 1.0 to 4.1 mg/L for ketodoxapram. The total drug concentrations (doxapram + ketodoxapram) were always >9 mg/L.[101] These high concentrations should not be observed in the future if recommended lower doses are used, and monitoring of plasma concentrations should aim to keep total drug concentrations under 4 mg/L as much as possible.

2.3. Miscellaneous

A few trials of drugs used as adjuvant and/or prophylactic therapies have been published, but these therapies have not yet been properly evaluated in the care of apnoeic neonates.

Antenatal betamethasone has been considered for the prevention of apnoeas of prematurity. Recent studies, published as abstracts,[112,113] suggest that betamethasone may actually have a significant maturational effect on the control of respiration, being beneficial on the incidence and the cessation of apnoea in premature infants. This would be in addition to the positive effects of prenatal maturation associated with betamethasone. The benefit of prenatal betamethasone on mortality and morbidity seems far above the risks of this treatment for the neonate.[114-117] However, caution must be taken in cases of repetitive antenatal glucocorticoid treatment because of the potential risks on immune system and neuromotor development.[117-119]

As acetazolamine reduces sleep apnoea in adults exposed to high altitude, it was compared with aminophylline in 14 preterm infants.[120] It was shown to increase the ventilatory response to CO_2 as did aminophylline, but it did not have any effect on apnoea incidence.

In another study,[121] a retrospective analysis of 16 cases of theophylline-refractory preterm patients given 10 to 15 mg/kg/d of oral primidone showed a significant decrease in apnoea (68 %) and in bradycardic events (69%) 24 hours after the initiation of primidone. The mean number of apnoea was 8.7±2.0 before primidone and 3.0±0.8 in the first day of treatment ($p < .01$). Bradycardic events decreased from 10.1±2.1 before treatment to 3.0±0.7 on the first day of treatment ($p < .005$). The same beneficial effects were observed for the 2 following days. Primidone has been shown to be efficacious in infants with neonatal seizure disorders,[122] and it was speculated that the apnoeic events represented some form of subcortical seizure activity.[121] This is out of the definition of 'idiopathic' apnoea and has not been investigated since then.

Methylsulfate diphemanyl has been proposed for the management of infants experiencing vagal hyperactivity leading to significant bradycardia.[123] Methylsulfate diphemanyl is a quaternary ammonium anticholinergic agent, with peripheral effects similar to atropine. Its adverse effects are numerous and may be dangerous: atrioventricular blocks, QT lengthening and torsades de pointes.[124,125] It relaxes the gastro-oesophageal sphincter and is therefore contraindicated in the management of sliding hiatus hernia but also in the case of significant gastrointestinal reflux. Its efficacy in preventing bradycardia and apnoeas linked to vagal hyperactivity has not yet been demonstrated.[126]

There are considerable interindividual variations in pharmacokinetic parameters in neonates and in premature infants.[127] The recommended adminis-

tration interval is 12 hours. The co-administration with drugs that lengthen corrected QT interval is contraindicated.[124] In any case, use of methylsulfate diphemanyl should be limited to a restricted number of selected neonates, only after 4 to 5 weeks of age to infants who are also over 35 weeks postconceptional age.[5,123]

3. Nonpharmacological Treatment of Apnoea

3.1 Nursing

Careful nursing is mandatory in preventing apnoea.[1,5] Because of hypotonic neck muscles, it is very important to prevent hyperextension or hyperflexion that may trigger obstructive or mixed apnoea. In addition, whenever possible, infants should be nursed in prone position when moderate respiratory distress related to bronchopulmonary dysplasia is present. Ventilation is actually improved by prone positioning, as is oxygen tension.[128] A shorter gastric emptying time and a decreased incidence of regurgitation and gastric aspiration have also been demonstrated.[129]

The Task Force of the American Academy of Paediatrics (1996) recommends a nonprone sleeping position for infants to prevent sudden infant death syndrome. This recommendation has been validated throughout the world for asymptomatic infants who have been discharged home from hospital care. However, these benefits (which could be related to alterations in sleep states with more awakenings[130]) may become deleterious in immature neonates with lung disease and is not necessary when the infants are in hospital and being continuously monitored. In addition, nursing in a moderately tilted position (15°) reduces hypoxaemic events in preterm infants.[131] This recommendation of prone nursing does not apply once the neonate has been discharged and has no advantage for preterm infants without lung disease.[132]

The thermal environment should be set to maintain a central temperature in the neutral zone, between 36.5 and 37°C. In addition, it has been demonstrated that keeping the thermal environment at the lower end of the neutral thermal range reduces apnoeas, compared with keeping the thermal environment in the upper end of the neutral thermal range.[133] Oxygen and air admixture should be warmed, humidified and administered by head-box since cold stimulation of the trigeminal area of the face has been shown to trigger reflex apnoea.[134,135]

Cutaneous stimulation may significantly decrease apnoea frequency,[136] probably by increasing external stimuli. Placing the infants on water- or rocking-beds results in labyrinthine stimulation, which reduces apnoea frequency.[1] However, these treatments are not very efficient on a long term basis and these infants often require further more vigorous therapeutic actions.[22]

3.2 Continuous Positive Airway Pressure

The effectiveness of CPAP is well established to help weaning from mechanical ventilation,[137,138] or as an alternative to conventional ventilation in selected neonates.[139,140] However, the advantages of CPAP are still controversial when the risk-benefit balance is taken into account besides preventing extubation failure.[141] In 13 premature infants showing bradycardia and/or desaturation events, Kurtz observed fewer obstructive apnoeas, more short central apnoeas and less severe associated desaturation during 2h of nasopharyngeal CPAP compared to a period of 2h without CPAP [142]. In another study[143], CPAP markedly decreased the incidence of mixed and obstructive apnoeas, in 14 preterm infants, during sequential 45-minute periods of observation, but central apnoea episodes were unaffected by CPAP. This has been confirmed by MacNamara and Sullivan[144]: 24 infants, 30 to 42 weeks gestational age (8 preterm, and 8 infants with anatomic upper airways abnormalities), referred from 1 to 51 weeks of postnatal age for obstructive sleep apnoeas, were treated with nasal CPAP which prevented obstruction and reversed sleep disturbances, studied by polysomnographic sleep recording.

Different mechanisms seem to be involved in the efficacy of CPAP for obstructive apnoea treatment: CPAP may stabilise the rib cage and so re-

duce inhibitory neural input to the respiratory control centre;[145] CPAP may reduce apnoeas by relief of upper airway obstruction, possibly via splinting of the pharyngeal airway[143] (this hypothesis being supported by the effectiveness of CPAP in the treatment of bronchomalacia[146]) and finally, CPAP may prevent hypoventilation by improving functional residual capacity and alveolar expansion, as suggested by the improvement in gas exchange.[143,147]

It is noteworthy that nasally applied CPAP has numerous advantages over CPAP provided via the endotracheal tube.[148] Nasal prongs are easy to apply and comparatively noninvasive to the airway.[149] In addition, a new technical device, the Infant Flow Driver®, may increase the usefulness of CPAP by further decreasing the work of breathing.[148,150,151] However, short term physiological effects are not obvious with this technique[152] and no clear advantage has been found versus conventional CPAP in infants with recurrent episodes of apnoea in the absence of lung disease.[153]

Different adverse effects have to be taken into account when using CPAP for the treatment of apnoeas in infants. Using CPAP may lead to an increase in the rate of pneumothorax from 6-10% to 15-20% for infants below 1500g at birth.[154] Even the use of nasal cannulas for oxygen delivery in preterm infants may lead to inadvertent administration of high positive end-distending pressure of up to 10 cmH_2O. This can induce gas trapping, inhibition of breathing and barotrauma.[155] Thus, caution must be advised to prevent pulmonary air-leaks.[156-158] In addition, high levels of nasal CPAP therapy may impair cardiac output.[159] Neonatologists should also be aware of the potential for local complications such as nasal deformity[160] or choanal stenosis.[161] A moderate but significant risk of CPAP treatment is gaseous bowel distension observed in about 30% of the infants.[162-164] This effect probably does not lead to necrotising enterocolitis but will prevent the premature infant from early feeding, which has been shown to be beneficial for development. Finally, glomerular filtration rate and urine output decrease significantly when high CPAP (above 5 cmH_2O) is applied,[165,166] and hyponatraemia also develops at very high CPAP levels (above 7 cmH_2O).[165]

In summary, nasal CPAP (2 to 5 cmH_2O) appears to be able to improve gas exchange, to stabilise compliant chest wall and to effectively treat obstructive or mixed apnoeas. However, low levels of CPAP should be used, and babies should be taken off CPAP as soon as possible[162] to prevent its adverse effects.

3.3 Conventional Mechanical Ventilation

When recurrent and severe apnoeas persist in spite of appropriate therapeutic attempts,[1] or in the case of intolerance of other treatments (for instance, infants below 1500g not doing well with CPAP[154]) it becomes necessary to initiate mechanical ventilation after endotracheal intubation. Triggered synchronized ventilation with minimal peak inspiratory pressure should be used to obtain stabilisation and minimise the risks of barotrauma. However, intubation by itself leads to physiological changes[149] and caution should be taken since inappropriate ventilation settings[167] or chest physiotherapy[168] may be associated with haemodynamic disturbances and brain damage. Weaning from the respirator should be considered after 4 to 5 days, as soon as the infant tolerates a rate at about 5 to 10 cycles per minute.[1,5]

4. Conclusion: Suggested Management of Apnoea

In performing a risk effectiveness analysis of therapies for apnoea in premature infants, the literature is marked by a general lack of reliable information regarding the risks associated with apnoea itself or the long term risks of treatment. Therefore, we can only propose what seems to be the most appropriate management given the current state of knowledge. It seems of crucial importance to establish precise diagnosis of the type of apnoea with documented monitoring, using monitors with hard copy and including pulse oximetry, and to evaluate potential implications of apnoeas before initiating any treatment.

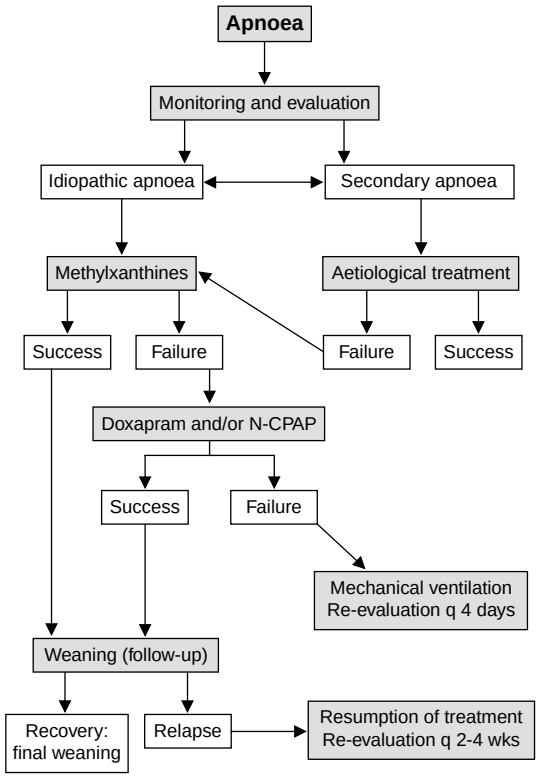

Fig. 1. Suggested management of apnoea. **N-CPAP** = nasally applied continuous positive airway pressure.

The first management step requires a thorough evaluation to look for possible treatable causes of secondary apnoea.[34] When no specific cause has been identified and severe apnoeic episodes continue, according to the risk-benefit analysis of the treatments available we would suggest beginning with methylxanthines, preferably caffeine. In the case of treatment failure or only partial success, additional treatment with doxapram could be used when hypoventilation is present, or nasal CPAP when upper airway instability or obstructive apnoeas are predominant. In the case of CPAP failure or intolerance, doxapram can be used as an alternative. In the case of continued treatment failure, a thorough re-evaluation is mandatory before deciding to undergo mechanical ventilation.

Close follow-up of the treatment, its efficacy and its tolerability are mandatory. Infants can be weaned from treatment 4 to 5 days after the disappearance of significant apnoea. Progressive weaning should start with the last treatment introduced. Continuous monitoring 4 to 5 days is required to detect any relapse of recurrent and severe apnoeas, which would lead to the resumption of the last treatment stopped[5] (fig. 1).

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