

Discussion

The enhanced urinary lactulose:mannitol excretion ratios observed in these three babies indicate a sudden increase in intestinal permeability to the larger marker, as has been described in children with active Crohn's disease.⁶ Enterocyte damage or loss may allow an abrupt and appreciable rise in lactulose uptake by increasing available paracellular pathways. Such a change is not reflected by an increased mannitol absorption, because the aqueous pore population by which only this smaller marker can pass is very large compared with the paracellular pathways available to both molecules.

Although hyperosmolar feeds have been incriminated in the pathogenesis of necrotising enterocolitis,¹ we think it highly unlikely that the markers were responsible for our findings, as the concentrations used were well within those present in many infant milk formulas.⁴ We suggest that although it is not known whether the passage of bloody stools in our babies represented incipient enterocolitis, the enhanced intestinal permeability described might well allow the absorption of other molecules, such as microbial antigens and toxins,

contributing to the devastating damage that characterises necrotising enterocolitis.

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Idiopathic apnoea of prematurity treated with doxapram and aminophylline

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SUMMARY Doxapram infusion was given to five preterm infants in whom therapeutic concentrations of theophylline had failed to control episodes of apnoea. Doxapram successfully controlled the apnoea, the arterial blood PCO₂ value decreased significantly, and no side effects were reported.

Apnoea of prematurity is a disorder frequently encountered in preterm neonates, and the hypoxia attributed to these attacks may threaten the integrity of the central nervous system. Since the introduction of aminophylline for the treatment of idiopathic apnoea of prematurity, the use of xanthines in various forms as respiratory stimulants has gained widespread acceptance. A considerable number of preterm infants with apnoea fail to respond satisfactorily, however, and require further measures

such as continuous positive airways pressure or mechanical ventilation.

Doxapram, an analeptic agent with wide safety margins, is an effective respiratory stimulant in adults¹ and has already been used to stimulate breathing immediately after birth² or to overcome idiopathic apnoea of prematurity.³ We describe the response to doxapram infusion in five preterm infants in whom episodes of apnoea persisted despite adequate treatment with aminophylline.

Patients and methods

Preterm infants in this hospital are routinely connected to heart and respiratory rate monitors. Apnoea is defined as cessation of breathing associated with cyanosis or with bradycardia (a fall of 40 bpm from basal heart rate). Idiopathic apnoea of immaturity is diagnosed by exclusion of treatable

Table 1 Patients with idiopathic apnoea of prematurity (IAP) treated with aminophylline

Case No	Sex	Weight (g)	Gestational age (wks)	Age at development of IAP (hrs)	Blood aminophylline concentration ($\mu\text{g/ml}$)
1	F	930	27	24	21
2	M	1130	28	24	19
3	F	575	25	27	19
4	F	795	27	72	13
5	M	950	28	24	10
Mean (SD)		876 (206)	27 (1.2)	34 (21)	

causes of apnoea (such as sepsis, hypoxaemia, patent ductus arteriosus, anaemia, etc) and preterm infants developing this are treated with aminophylline if the frequency of attacks is four or more over an 8 hour period.

Five preterm infants (Table 1) in whom apnoeic attacks persisted despite therapeutic blood concentrations of theophylline,⁴ received additional treatment with doxapram infusion at a constant rate of 2.5 mg/kg/hr for 48 hours. The combined treatment was considered successful if apnoeic episodes stopped within that time. Arterial blood gases were monitored at least every four hours in infants receiving oxygen treatment and every 24 to 48 hours in those breathing room air.

Results

Giving doxapram to five preterm infants who had received an adequate dosage of aminophylline controlled the apnoeic episodes in all cases. Complete control was achieved after 4 to 32 hours of continuous infusion (Table 2). Three of the five infants developed recurrent episodes of apnoea within 8 to 24 hours after doxapram infusion was stopped—two received a second course, after which episodes of apnoea were rare, but the third infant (case 1) required three courses (the last one was extended to 72 hours). The Paco_2 values were significantly lower when on doxapram infusion than

beforehand ($P < 0.05$ paired student's *t* test). There were no side effects in any of the patients, even though one of the infants (case 1) had inadvertently received 5 mg/kg doxapram over two hours.

Discussion

Doxapram was useful in controlling idiopathic apnoea of prematurity unresponsive to aminophylline alone. Since both drugs are known to stimulate the respiratory centre, the additional effect of doxapram may indicate the existence of different pathways by which each drug activates the respiratory centre. Doxapram can activate the respiratory centre by a direct action or through the carotid body chemoreceptors.⁵ In an animal model doxapram was shown to operate better when Paco_2 values were above the normal range.⁶ The high Paco_2 values in four of our five patients receiving aminophylline, and the subsequent decrease in all of them while on doxapram infusion, may suggest a similar effect in humans. The success of giving doxapram to our apnoeic preterm infants who had been given aminophylline does not mean that doxapram is superior to aminophylline, or that it should replace this drug as a first choice in treating idiopathic apnoea of prematurity, or that all those preterm infants that have persistent episodes of apnoea despite adequate concentrations of theophylline will respond. Nevertheless, if some of these patients respond, more

Table 2 Response to doxapram treatment

Case No	No of apnoeic episodes while on aminophylline (8 hrs)	Paco_2 before doxapram (kPa)	Paco_2 while on doxapram (kPa)	Time to full response (hrs)
1	10	6.40	5.33	4
2	8	6.26	5.33	22
3	5	7.19	5.06	6
4	9	6.40	4.53	32
5	4	5.33	4.66	6
Mean (SD)	7 (3)	6.26 (0.67)*	4.93 (0.40)*	14 (12)

* $P < 0.05$, paired *t* test.

invasive techniques such as continuous positive airways pressure or mechanical ventilation will be avoided, which may be important in units lacking personnel and technical means of ventilatory support.

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