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Effect of aminophylline on brain stem auditory evoked potentials in preterm infants

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Abstract

To determine the neurophysiological effects of aminophylline on apnoea of prematurity, the brain stem auditory evoked potentials (BAEPs) of 30 apnoeic infants and 34 age matched controls were evaluated and compared. After six days of treatment with aminophylline, the brain stem conduction time (interpeak latency of I–V) in apnoeic infants decreased compared with controls of a similar postconceptional age. The mean latencies of the peaks and interpeaks of all waves except wave I were significantly lower in the apnoeic infants after than before receiving aminophylline. No significant differences were found in the latencies of BAEPs between the apnoeic infants who responded and those who did not respond to aminophylline treatment, however. These results suggest that aminophylline may enhance conduction along central auditory pathways and stimulate the regulatory effect on the respiratory centre of the brain stem.

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Recurrent apnoea often occurs in preterm infants and the incidence of apnoea in these infants is inversely correlated with their gestational age.[1] Apnoeic episodes also increase with decreasing birth weight.[2] The origin of apnoea in premature infants appears to be related to an immaturity of the central respiratory control mechanism, as reflected by a lack of dendritic arborisation and a decreased number of synaptic connections in the central nervous system (CNS).[3 4] Such idiopathic apnoeic spells are successfully treated with xanthine derivatives such as aminophylline,[3 5] caffeine,[6–8] and theophylline.[6 8]

The major effect of xanthine on the CNS is to increase the activity of the depressed respiratory centre.[4] Several studies have investigated the effects of theophylline on the CNS using electrophysiological tests, including electroencephalography (EEG), somatosensory evoked potentials, F waves, and long loop reflexes in patients with asthma and normal volunteers.[9–11] The effects of aminophylline on serial brain stem auditory evoked potentials (BAEPs) in preterm infants with apnoea have not previously been reported.

There is a correlation between the frequency of apnoea in preterm infants and neurological maturation as estimated by evoked potentials.[12] Serial BAEPs are thought to be useful in detecting the apnoeic episodes in infants with 'near miss' sudden infant death syndrome.[13] This study was conducted to evaluate the neurophysiological effect of aminophylline on apnoea using BAEPs and to determine the differences in electrophysiological findings between infants with and without apnoea at the same postconceptional age.

Subjects and methods

Over a period of two years, 64 consecutive preterm infants who either had apnoea or had no apnoea within the first week of postnatal life were selected for the study. The criteria included for the study were: (a) gestational age between 28 and 33 weeks as determined by the Dubowitz *et al* criteria[14]; (b) no congenital anomalies; (c) uncomplicated pregnancy and delivery; (d) Apgar score of 7 or more at five minutes; and (e) uneventful neonatal course except for apnoea. In this study, apnoea was defined as recurrent episodes of breathing stopping for 20 seconds or more, or for less than 20 seconds associated with bradycardia (heart rate $\leq$80 beats/minute). During the study period, 30 infants had apnoea (group I) and 34 infants had no apnoea (group II). Apnoea was detected using a cardiorespiratory impedance monitor with an alarm (Model 78354A, Hewlett Packard). Once the infant had apnoea, he or she was treated first with tactile stimulation or occasionally with mask bagging. If the infant did not respond, aminophylline treatment was started. Aminophylline was administrated intravenously with a loading dose of 5 mg/kg, followed by a maintenance dose of 2 mg/kg every 12 hours for six days. Serum aminophylline concentrations were measured in group I infants one hour after the fourth and tenth dose of aminophylline. An effective response was defined as decreasing the frequency of apnoea to less than half within 24 hours of administration. If the infants did not respond to aminophylline treatment and still had frequent apnoea, intermittent positive pressure ventilation was initiated. Serial BAEPs were measured for all infants at regular intervals. The BAEPs was first examined within 48 hours after birth, then repeated within the first week, and then each week until discharge. The study was approved by the human ethics committee of the hospital and consent was obtained from the parents of each infant.

BRAIN STEM AUDITORY EVOKED POTENTIALS

The BAEPs were examined in a quiet room without sedation. The stimulus was a 100 μs click presented monaurally through a shield

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Table 1 Clinical data

Characteristics	*Apnoea group (n=30)*	*Control group (n=34)*	*p Value*
Sex (male/female)	17/13	18/16	NS
Mean (SD) birth weight (g)	1555 (330)	1637 (284)	NS
Mean (SD) gestational age (weeks)	30·9 (1·7)	31·1 (1·4)	NS

NS=not significant.

Table 2 Number of infants grouped according to frequency of apnoeic attacks each day before and during treatment with aminophylline

Frequency of apnoea (episodes/day)	*Before treatment*	*Days after treatment*					
		1	*2*	*3*	*4*	*5*	*6*
≤2	0	3	6	16	20	18	20
3–10	16	21	17	8	6	8	7
11–19	11	2	3	3	2	3	2
≥20	3	4	3	3	2	1	1

earphone (TDH-49P). Alternating phase clicks were used to elicit the response in this study. The stimuli were presented to the subjects at a rate of 13·1 each second and with an intensity of 70 dBnHL. The non-stimulated ear was masked for white noise. Silver chloride electrodes filled with conducting paste were applied to the vertex and the mastoids with the interelectrode impedance less than 5000 ohms. A midfrontal electrode served as the ground electrode. Bipolar EEG activity was recorded from an amplifier with a filter band pass of 100–3000 Hz. At least two sets of 2048 averaged responses, in which the peaks were clearly detectable, were obtained from each ear and were summed by a signal averager (Medelc MS 25). The analysis time was 20 ms from the onset of stimulus. Peak latencies for the prominent peaks labelled as wave I (representing VIII nerve activity) and V (representing midbrain activity), and the interpeak latency I–V (brain stem conduction time) and the V/I amplitude ratio were measured.

DATA ANALYSIS

The paired data were compared using the Wilcoxon signed rank test; other unpaired data were analysed by the Mann-Whitney test. The wave latencies in apnoeic infants before, during, and after treatment with aminophylline were compared by the Friedman test. A p value of $<0·05$ was considered significant.

Results

Table 1 summarises the clinical data obtained from the two groups. Both groups had comparable sex distribution, birth weight, and gestational age. Seven infants in group I and six in group II had hyperbilirubinaemia (peak serum bilirubin >171 μmol/l). None of the infants had hypoglycaemia, CNS anomalies, intraventricular haemorrhage, nor sepsis.

The mean steady state serum aminophylline concentration was 8·9 μg/ml (range 6·4–12·0 μg/ml) in group I. There was no difference in serum aminophylline concentrations between the infants who showed a response and those who did not (8·6 (1·6) and 9·9 (2·2) μg/ml respectively). None of the infants in group I had signs of aminophylline toxicity.

The frequency of apnoea was categorised based on the number of episodes of apnoea each day. Table 2 gives the number of infants in each category before and during aminophylline treatment. It is clear that after aminophylline treatment more infants showed less episodes of apnoea. The mean (SD) number of apnoeas decreased significantly from 11·2 (8·9) (episode/day) before aminophylline to 4·2 (6·9) at the end of six days of treatment. Similarly, the mean (SD) number of bradycardias decreased from 12·4 (11·2) (episode/day) before treatment to 2·7 (3·7) after six days of treatment.

Table 3 compares the initial brain stem conduction time obtained within 48 hours of birth between the two groups of infants. The brain stem conduction time, interpeak latency I–V, was significantly longer in group I than in group II infants regardless of postconceptional age. Table 4 compares the differences of the mean latencies and standard deviation of the initial and last BAEPs between group I and group II at various ages. The initial BAEPs were obtained about 48 hours after birth and before the first dose of aminophylline, whereas the last BAEPs were obtained in group I at about 24 hours after the last dose of aminophylline and in group II at about the same postconceptional age of 7 days. Infants in group I had significantly greater reduction in latency V and in interpeak latency I–V than infants in group II regardless of postconceptional age. There was no significant difference between the groups in peak I latency. There was also no significant difference in the amplitude ratio of wave V/I between the groups.

Aminophylline was found to be effective in decreasing the frequency of apnoea in 22 (73%) of the 30 infants in group I. A significant reduction in the latencies of peak V and interpeak I–V (during and after treatment compared with before treatment) was observed in the 22 aminophylline treated infants in whom the treatment was successful ($\chi^2=18·43$, $p<0·001$; $\chi^2=23·38$, $p<0·001$) and in the eight infants in whom it was ineffective ($\chi^2=12·25$, $p=0·002$; $\chi^2=7·93$, $p=0·019$). These two groups of infants had similar wave latencies whether the measurements were made before, during, or after aminophylline treatment.

Table 3 Comparison of the initial brain stem conduction time (I–V interpeak latency) obtained within 48 hours after birth in 64 preterm infants. Values are mean (SD)

Postconceptional age (weeks)	*Apnoea group*		*Control group*	
	No of infants	*I–V interpeak latency (ms)*	*No of infants*	*I–V interpeak latency (ms)*
28–29	5	6·0 (0·4)	3	5·6 (0·1)*
30–31	17	5·9 (0·3)	18	5·5 (0·2)**
32–33	19	5·6 (0·2)	24	5·4 (0·2)*
34–35	17	5·5 (0·4)	21	5·2 (0·2)*

*p<0·05; **p<0·005 by the Mann-Whitney test.

Discussion

A strong relation between long brain stem conduction times for the BAEPs and clinical

Table 4 Comparison of the differences in the mean latencies (in ms) of initial and last brain stem auditory evoked potentials (BAEPs) between apnoeic infants (group I) and control infants (group II) at various postconceptional ages. Values are mean (SD)

BAEPs	Initial (1)	Last (2)	Difference (1)–(2)	p Value*
28–29 Weeks				
Peak I latency (ms)				
Group I (n=5)	2·8 (0·5)	2·8 (0·5)	0 (0·4)	
Group II (n=3)	2·7 (0·2)	2·6 (0·2)	0·1 (0·1)	0·29
Peak V latency (ms)				
Group I (n=5)	8·8 (0·4)	8·0 (0·4)	0·7 (0·2)	
Group II (n=3)	8·3 (0·2)	8·1 (0·2)	0·2 (0·1)	0·025
Interpeak I–V latency (ms)				
Group I (n=5)	6·0 (0·4)	5·2 (0·5)	1·0 (0·7)	
Group II (n=3)	5·6 (0·1)	5·6 (0·2)	0·1 (0·2)	0·025
30–31 Weeks				
Peak I latency (ms)				
Group I (n=13)	2·7 (0·4)	2·7 (0·3)	0 (0·4)	
Group II (n=15)	2·2 (0·1)	2·1 (0·2)	0 (0·2)	0·61
Peak V latency (ms)				
Group I (n=13)	8·7 (0·5)	7·9 (0·4)	0·8 (0·4)	
Group II (n=15)	8·0 (0·2)	7·7 (0·2)	0·3 (0·2)	0·002
Interpeak I–V latency (ms)				
Group I (n=13)	6·0 (0·2)	5·2 (0·4)	0·8 (0·4)	
Group II (n=15)	5·8 (0·1)	5·5 (0·1)	0·2 (0·2)	<0·0001
32–33 Weeks				
Peak I latency (ms)				
Group I (n=12)	2·6 (0·2)	2·5 (0·3)	0·2 (0·3)	
Group II (n=16)	2·2 (0·4)	2·1 (0·2)	0·1 (0·2)	0·54
Peak V latency (ms)				
Group I (n=12)	8·4 (0·2)	7·8 (0·4)	0·6 (0·4)	
Group II (n=16)	7·8 (0·3)	7·5 (0·2)	0·3 (0·2)	0·017
Interpeak I–V latency (ms)				
Group I (n=12)	5·8 (0·2)	5·3 (0·4)	0·4 (0·3)	
Group II (n=16)	5·6 (0·2)	5·4 (0·1)	0·1 (0·2)	0·008

*Mann-Whitney test.

apnoea in preterm infants had been reported.[12] In this study, we used serial BAEPs to assess the effect of aminophylline on apnoea of prematurity by comparing the wave latencies in preterm infants with apnoea before and after treatment. In addition, the changes of these BAEPs were compared with those of infants without apnoea at a similar postconceptional age. Our results showed that the interpeak latency I–V was longer in apnoeic infants than in the control infants at a similar postconceptional age of 28–35 weeks. This result is consistent with previous reports.[12 15 16] In this study, the risk factors, including asphyxia, intracranial haemorrhage, severe neonatal jaundice, and CNS infections, which are associated with an alteration of the BAEPs were excluded. Thus the prolongation of brain stem conduction times may be caused by the immaturity of the respiratory centre on the brain stem. After aminophylline treatment the decrease in interpeak latency I–V in apnoeic infants was significantly greater than that in age matched control infants at the same period ($p<0·05$). With regard to the clinical efficacy of aminophylline on apnoea, however, no significant difference in wave latencies was found between the groups in which treatment was effective and ineffective. Thus our results suggest that aminophylline probably had an enhancing effect on the central auditory conduction.

Pelliowski and Finer reported that theophylline caused a significant reduction in the incidence of apnoea; however, the effect did not last for more than one week.[6] Gerhardt *et al* observed that 48 hours after starting treatment with aminophylline, the incidence of apnoeic episodes decreased from 29·7 to 4·4 in 24 hours.[5] In our study, similar results were found: the frequency of apnoea and bradycardia in apnoeic infants was markedly reduced within one week of the administration of aminophylline. Furthermore, we found a significant shortening of the mean latencies of peak V and interpeak I–V in apnoeic infants after aminophylline treatment ($p<0·005$). This result could be related to the maturation of the brain stem with advancing postconceptional age, or the drug effect of aminophylline. Maturational trends in BAEPs have been well documented.[15] From birth to 4 years of age, a progressive shortening in wave latencies has been attributed to normal myelogenesis development.[17] In this study, the interpeak latency I–V after six days of aminophylline treatment decreased markedly in infants with apnoea at postconceptional ages of 28–33 weeks. Moreover, the decrease in interpeak latency was greater in the group treated with aminophylline than that of age matched controls at the same postconceptional age. Therefore the effect of aminophylline on BAEPs in premature infants with apnoea cannot only be explained by the maturational effect of advancing age. Thus the decrease in brain stem conduction time may result from the enhancement of the stimulatory effect on the respiratory centre by aminophylline.

The precise mechanism by which aminophylline affects the clinical course of apnoea of prematurity is still unknown. Aminophylline may increase the sensitivity of medullary respiratory centres to carbon dioxide,[5 7] increase afferent nerve traffic to the brain stem,[3] and inhibit cerebral adenosine receptors.[8] It was thought that direct stimulatory action on the respiratory and vasomotor centres results in the increase in the rate and depth of breathing.[7] This study shows that aminophylline may decrease the brain stem conduction time, at least over six days of treatment. This result is inconsistent with the report by Henderson-Smart *et al* in which six preterm infants received theophylline without an obvious change in brain stem conduction time during or after withdrawal of the drug.[12] These conflicting findings may be due to the differences in methodology. Only a small number of infants received theophylline in the Henderson-Smart *et al* study; furthermore, the dose and duration of theophylline treatment was not described clearly. Therefore, previous studies cannot be compared with our results.

The central effects of theophylline have been evaluated using several neurophysiological tests. Bartel *et al* reported that the changes in EEGs and F waves are compatible with the stimulatory effects in the brain and spinal cord induced by 15 weeks of theophylline treatment in young normal volunteers.[9] No evidence for cortical hyperexcitability was found in these subjects using somatosensory evoked potentials and C responses, however.[9] The EEG findings after theophylline treatment may be related to the duration of drug treatment. The amplitudes of the alpha waves were significantly lower in long term treatment,[9] whereas an increase in the frequency of alpha waves was observed after the administration of

a single dose.[11] Theophylline is well tolerated in adults and the long term use of this drug is possible, whereas in premature infants theophylline may result in several adverse effects and its dose and the duration of treatment should be monitored with caution. As BAEPs may reflect the activity of the brain stem auditory pathway, including the auditory brain stem nuclei which lie close to the respiratory centre, BAEPs may be more helpful in evaluating the effect of aminophylline on the respiratory centre than other neurophysiological tests.

In conclusion, the neurophysiological effect of aminophylline in preterm infants with apnoea may mainly be on the respiratory centre of the brain stem, making the regulation of breathing more effective.

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