

EFFECT OF SERUM CAFFEINE LEVEL ON PNEUMOCARDIOGRAM OF PREMATURE INFANTS TREATED FOR APNEA WITH THEOPHYLLINE

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ABSTRACT

It is speculated that measurement of serum theophylline concentration alone, without concomitant caffeine level determination, may lead to a false negative (normal) pneumocardiogram due to possible existence of therapeutic caffeine level resulting from the methylation of theophylline. Treatment of neonatal apnea with theophylline as documented by a normal follow-up pneumocardiogram should be considered successful only when the levels of both theophylline and caffeine have been documented subtherapeutic at time of re-test.

INTRODUCTION

Effective treatment of apnea of prematurity can be accomplished with the administration of theophylline (1) or caffeine (2). Assessment of the effectiveness of theophylline therapy in managing apnea of prematurity (3) can now be performed utilizing the pneumocardiogram (4, 5), a 12 hour recording of respiration and heart rate on magnetic tape. Therapeutic serum concentration of theophylline in the range of 7-15 $\mu\text{g/ml}$, and of caffeine as low as 3-4 $\mu\text{g/ml}$ can abolish apnea and regularize neonatal breathing patterns (6). It has been documented that interconversion of theophylline and caffeine in the newborn infant (7), with a considerably higher ratio of caffeine to theophylline in neonates treated with theophylline (8) when compared to the ratio of theophylline to caffeine in neonates treated with caffeine (9). It is possible that the reported efficacy of low dose theophylline therapy (10) with lower theophylline plasma concentrations (2.8-4.8 $\mu\text{g/ml}$) is due to the potentiating effect of unmeasured caffeine concentration resulting from methylation of theophylline. Measurement of theophylline level alone is therefore insufficient in monitoring the clinical course of the

premature infant with apnea and determination of serum caffeine level should also be included as these two methylxanthines are both pharmacologically active.

CURRENT MANAGEMENT PROTOCOLS

Infants with abnormal pneumocardiogram are started on theophylline with a loading dose of 6 mg/kg. Maintenance dose is 2 mg/kg given initially every 12 hours. The maintenance dose is adjusted according to the serum theophylline level (8-10 µg/ml) and sometimes given every 8 hours. The pneumocardiogram is repeated when the therapeutic range of serum theophylline concentration has been attained. The subsequent management of these infants depends on the result of this repeat pneumocardiogram and can be categorized as follows.

Abnormal Pneumocardiogram Despite Medication

Infants whose pneumocardiogram remains abnormal despite adequate serum theophylline level undergo further evaluation, including an electroencephalogram, and are treated with phenobarbital when indicated. The parents of these infants are instructed in the use of a home apnea monitor and proper performance of cardiopulmonary resuscitation before the patient's discharge. These infants are followed in the neonatal clinic and monitored for any evidence of theophylline toxicity. The medication dose of infants treated with phenobarbital is adjusted to maintain a normal serum drug level. The majority of infants are successfully discontinued from the theophylline therapy and the home apnea monitor in four to six months and are asymptomatic on phenobarbital alone. Duration of phenobarbital therapy varies depending on the infant's clinical course.

Normal Pneumocardiogram on Medication

Infants whose apnea has responded to administration of theophylline, as evidenced by a normal pneumocardiogram on repeat test, are sent home on medication without a home apnea monitor. After 4-6 weeks, the theophylline therapy is discontinued for approximately 72 hours while the infant is on an apnea monitor. When the theophylline level is determined to be subtherapeutic or near zero, a repeat pneumogram is performed. If the pneumogram is abnormal, theophylline is resumed until a therapeutic level is attained and the infant has a normal repeat pneumocardiogram. The infant is maintained on medication for another 1-2 months. The duration of treatment with theophylline has been variable but these infants usually have normal pneumocardiograms when theophylline is discontinued at about 44 weeks conceptional age.

Normal Pneumocardiogram when Medication is Discontinued

Infants whose repeat pneumocardiogram is normal after the theophylline has been discontinued for about 72 hours, with serum theophylline level near zero, are considered to be resolved of apnea.

HYPOTHESIS

The concern and subject of this presentation are the infants who have normal repeat pneumocardiograms after discontinuation of theophylline when the infant is shown to have a subtherapeutic serum theophylline level. It is speculated that measurement of serum theophylline concentration without concomitant caffeine level determination may lead to a false negative (normal) pneumocardiogram due to the possible existence of a therapeutic caffeine level resulting from the methylation of theophylline. It has been shown that premature newborns have a remarkably slow elimination of theophylline (14-57 hours) and caffeine (40 - 231 hours). Bory et al (9) have found theophylline to disappear from the plasma three days after cessation of therapy, whereas caffeine was still present nine days after therapy. Continued formation of caffeine after the cessation of theophylline therapy could also result in a higher caffeine concentration.

CONCLUSION

Reliance on a subtherapeutic or near zero serum level of theophylline alone without a concomitant subtherapeutic level of caffeine may render the results of the follow-up pneumocardiogram unreliable. Treatment of neonatal apnea with theophylline as documented by a normal follow-up pneumocardiogram should be considered successful only when the levels of both theophylline and caffeine have been documented subtherapeutic at the time of re-test. We are presently utilizing a micro scale method using high performance liquid chromatography (HPLC) in the measurement of both theophylline and caffeine concentrations. Our recent capability to determine the levels of these two methylxanthines will allow us to test the hypothesis I have presented.

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