

Rationale for the use of aminocaproic acid for the prevention of pneumothorax associated intraventricular hemorrhage in the premature infant

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Intraventricular hemorrhage (IVH) is a frequent occurrence in the small premature infant which carries with it the potential of significant neurologic sequelae.¹ Recently it has been shown that IVH occurs in association with pneumothorax,^{2,3} with such close temporal relation as to suggest that pneumothorax is a definite etiologic factor in the development of IVH.⁴ It would be of value to have a medication which could be given at the time of recognition of a pneumothorax which would inhibit the development of an IVH. Aminocaproic acid may be such a medication.

Aminocaproic acid is a fibrinolysis inhibitor⁵ which has been shown to be effective in the control of hemorrhages in the following clinical situations: hemorrhage following prostatectomy,⁶ hemorrhage from chest tube drainage after cardiac surgery,⁷ dental extractions and surgical procedures in hemophilic patients,⁸ various uterine hemorrhages,⁹ hemorrhagic cystitis,¹⁰ and excessive fibrinolysis.⁵ The value of aminocaproic acid in the prevention of rebleeding from intracranial aneurysms is controversial.¹¹ Aneurysms are located primarily at the bifurcations of the large intracranial vessels, are subjected to high blood flow rates and systemic arterial pressures. Neither of these factors apply to the germinal matrix, a structure, which although richly vascular, is not a high flow structure.¹² Also, the systemic arterial and venous pressures in the newborn are much lower than those in the adult. Thus, the anatomic and physiologic differences between the neonate and the adult are so great that the aneurysm related experience with aminocaproic acid is not applicable to IVH in the newborn. The experience listed above in the control of primarily venous hemorrhage with the use of aminocaproic acid is more

applicable to the neonate.

The use of a fibrinolysis inhibitor may be of particular value in the prevention of IVH since the germinal matrix has a high concentration of fibrinolytic activity due to the presence of local plasminogen activators.¹³ These fibrinolysis inhibitors may account for the observed "saltatory" or progressive hemorrhages seen in a number of neonates,¹⁴ as well as the lack of containment of a large proportion of these hemorrhages to within the germinal matrix itself. Furthermore, there is evidence for platelet dysfunction and prolonged bleeding time in premature infants who develop IVH--factors which may in part be compensated for by the use of aminocaproic acid.¹⁵

Before using a new medication in ill premature infants, it is important to investigate its effect on bilirubin binding to albumin. Dr. Edouard Viollier, who is currently working in the clinical chemistry laboratories of the Mayo Clinic, using a fluorometric technique, was unable to demonstrate any change in bilirubin binding to albumin with concentrations of aminocaproic acid up to 100 mg/dl* (the therapeutic level in adults is 13 mg/dl). This finding corroborates one previously published report which stated that aminocaproic acid "appears not to be bound to plasma proteins".¹⁶

The literature experience with the use of aminocaproic acid in the neonate is limited to only one report. A 1650 gram, 31 week gestational age infant was treated with intravenous aminocaproic acid for generalized bleeding secondary to hyperfibrinolysis.¹⁷ The dose of aminocaproic acid used peaked at 121 mg/kg/hr for a total of 6 hours. The entire therapy program lasted 40 hours,

*unpublished results

without noted adverse effects.

There are several reported significant complications from the use of aminocaproic acid. These have included myocardial infarction,¹⁸ cerebral infarction,¹⁹ and hypotension and cardiac arrhythmias (with large and rapid intravenous injections).⁵

A myopathy has been described with prolonged oral use of this medication.^{20,21} Theoretically, a plasminogen inactivator may facilitate the accumulation of fibrin within the alveolar space and thus worsen respiratory distress syndrome which may be present.²²

In formulating a methodology to investigate aminocaproic acid's effectiveness in the prevention of pneumothorax associated IVH, several preliminary considerations must be met. (1) The temporal association between pneumothorax and IVH should be confirmed and further defined. Once the elapsed time from occurrence of pneumothorax to IVH is reliably established, the times of initiation and duration of use of aminocaproic acid could be defined. (2) Since aminocaproic acid is cleared by renal filtration,²³ it would be necessary that the infant demonstrate adequate urine output prior to initiation of therapy. (3) Therapeutic levels of aminocaproic acid have been defined in the adult as 13 mg/dl (the level at which plasminogen is inactivated,²⁴ and which is clinically effective²⁵), which may or may not be appropriate in the newborn. With the assumption that these same levels would be adequate, it would be necessary to have laboratory facilities available to determine the drug concentration. (An indirect method of assaying the effectiveness of aminocaproic acid would be to measure the thrombin time which should be affected by this medication. The Mayo hematology laboratories only require approximately 0.1 ml of blood

for this determination.) (4) Recent reports have indicated the effectiveness of phenobarbital²⁶ and ethamsylate²⁷ in the prevention of IVH in the neonate. This information gives reason to suspect that other medications, such as aminocaproic acid, may likewise be of value in selected circumstances. However, these observations raise questions as to the best method that should be employed to study aminocaproic acid--as a single medication, or as an adjunct to one of these other medications. (5) The investigation would have to be conducted in a controlled fashion after obtaining parental informed consent. (6) Attention to possible complications of therapy, frequent head ultrasound scans, and careful follow-up of all treated infants would have to be assured.

Footnotes

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