The recently published ECASS-III study examined the safety and efficacy of intravenous (IV) recombinant tissue plasminogen activator (rt-PA) in adult patients with acute ischemic stroke (AIS) up to 4.5 hours from symptoms onset. As neurologists endeavor to explore new therapeutic options in AIS, a question that lingers is whether they could safely administer IV rt-PA to children who present with an arterial AIS within the three-hour window. The most recent publication of the guidelines for management of stroke in children does not provide a clear indication or a road-map for administration of this medication in pediatric stroke patients.

Subsequently, the utility of IV rt-PA in childhood AIS remains enigmatic due to safety concerns, lack of an administration protocol, and more importantly, absence of a randomized controlled trial. In spite of this, one study reported that between 2000 and 2003, 1.6 percent of children presenting with AIS received thrombolytic therapy.

Although the landmark NINDS rt-PA Stroke Study enrolled patients between ages 18 and 80, current guidelines in early management of AIS in adults do not necessarily specify an age limit for IV rt-PA therapy. Since the US Food and Drug Administration’s (FDA) approval of IV rt-PA in adult AIS (1996), there have been several case reports or series published over the years examining this treatment option in children. The largest case series involved 29 consecutive children treated with 0.5 mg/kg of IV rt-PA at Toronto’s Hospital for Sick Children. The rate of thrombolysis was 79 percent, but almost one-fourth of these children suffered hemorrhage that required transfusion. A review by Carpenter and colleagues identified 44 children who received IV or intra-arterial rt-PA. However, only three of the children who received IV rtPA experienced clinical improvement. Eight additional case reports expressed good neurological recovery in children after undergoing IV thrombolysis for AIS.

What We Know
Despite the paucity of information regarding the use of thrombolytics in children with AIS, there is sufficient data with adult patients to suggest that this therapy could possibly be adapted for selected children. However, there is still a noticeable degree of hesitation in using IV rt-PA in children, and this is due to several factors. First, arterial AIS is much less common in children than in adults, and the odds of encountering a “stroke mimicker,” such as (among others) Todd’s paralysis or acute demyelinating encephalomyelitis (ADEM), is higher. Uncertainty in diagnosis surely creates a delay in treatment. This is in face of the fact that there is already a significant pre-hospital and in-hospital delay in diagnosis of AIS in children, sometimes up to 12 hours. The history could, however, be invaluable in delineating a vascular etiology or otherwise.

Second, the etiologies and patho-physiological mechanisms of AIS in children are quite diverse and do not necessarily parallel those of adults. There are recognized causes of AIS in children that are clearly not due to thrombosis, therefore administration of IV rt-PA may not deliver the desired benefit. For this reason, it is crucial to judiciously select patients based upon the underlying etiology.

Third, a child’s hemostatic physiology is different than an adult’s and, hence, response to therapy and risk of complications may potentially be different. With this in mind, one may wonder if there should be a minimum age limit below which IV rt-PA may not deliver the desired benefit. For this reason, it is crucial to judiciously select patients based upon the underlying etiology.

Fourth, if the decision to administer IV rt-PA in a child with AIS is finalized, there exists no standard protocol for an appropriate dose or duration of infusion. Finally, ethical ramifications of treatment come into play.

Considering Options
Since our information on thrombolysis in children is limited, how can we provide a convincing rationale to parents in order to obtain...
their agreement to therapy? The aforementioned factors only touch the surface of the matter and are perhaps the tip of the iceberg. Still, it is reasonable to at least consider the option, only if it is based upon a well-defined and thoroughly-navigated rationale. Selection of patients based upon various factors including age and the underlying stroke mechanism cannot be overemphasized. Once again, the history can assist us in at least determining whether or not the acute neurological deficit is vascular or better yet, thrombotic in etiology. If performed on-time, magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) may shed some light on this, confirming an AIS or cerebral artery occlusion. However, obtaining these tests emergently may not be possible at all centers.

What about the age limit? Because plasminogen concentrations reach levels compatible with adults after the age of two years, administration of IV rt-PA should perhaps be avoided in children less than this age. Then comes the administration protocol: could the standard 0.9 mg/kg dose in adults be as safe and efficacious in children? Fundamentally, neurologists may refer to the study involving the largest number of cases and utilize the protocol by which an IV dose of 0.5mg/kg was given, keeping in mind the high risk of hemorrhage. However, it must be entertained that to this date, the optimal IV dose for rt-PA in children remains unclear and the 0.5mg/kg dose may still have more risk than benefit.

Additional Considerations
Considering what is available, the decision to implement IV rt-PA therapy in children needs to be made on a case-by-case basis and of course, with parental consent. Parents need to be provided with clear information on the risks and possible adverse sequelae of therapy. They also should be informed of the rarity of data on the efficacy and the benefit of IV rt-PA in childhood AIS. Conversely, long-term consequences of stroke, including death (estimated at 10 percent), need to be discussed. Overall, the final decision of administering IV rt-PA to a child with AIS lies upon his or her parents. However, suggestion of this therapy to parents requires establishment of acute thrombosis as the cause of AIS. A child with an AIS due to cardiac thrombembolism is more likely to benefit from treatment than one with AIS due to migraine or cerebral hypoperfusion resulting from moyamoya. There has to be a pre-existing “thrombus” in order for thrombo-lysis to take place.

Under the right circumstances, a randomized clinical trial is feasible and perhaps long overdue. The design of such a trial with respect to safety and dose-finding has been suggested by Whelan and colleagues. This proposal suggests combining phases I and II in order to avoid the more time-consuming and expensive conventional approach. An interest in development of such a study certainly exists, although the process of conducting randomized controlled trials in pediatric subjects is perhaps more complex than in adults. Until more concrete evidence materializes, the administration of IV rt-PA in childhood AIS is purely investigational, and the decision to apply this treatment must be judged against a multitude of etiological, patho-physiological, and ethical conundra. PN

Dr. Behrouz has no relevant disclosures.

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February 2009 Practical Neurology 11