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STROKE:

Thrombolysis in childhood arterial ischemic stroke

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Abstract

Thrombolytic therapy is often used to treat arterial ischemic stroke in children, despite lack of FDA approval in this age group. The International Pediatric Stroke Study investigators have assessed the extent and nature of recombinant tissue plasminogen activator use in children in their registry, and have compared their findings with previously published case reports.

Awareness of arterial ischemic stroke in children is gradually increasing. Thrombolytic therapy has not been approved by the FDA for use in this age group, and American Heart Association guidelines published in 2008 suggest that thrombolysis should not be administered to children, although the recommendation is less strong for adolescents.¹ Some children, however, have received off-label recombinant tissue plasminogen activator (rtPA; also known as alteplase) for ischemic stroke, and several case reports have been published, mostly reporting favorable outcomes. A 2007 study by Janjua *et al.*, using administrative data from the Nationwide Inpatient Sample (representing 20% of all community hospital admissions in the US), found that between the years 2000 and 2003, 2,904 children were given a discharge diagnosis of ischemic stroke, and 46 (1.6%) of these had a procedural code for thrombolytic therapy.² Now, in a study published in *The Lancet Neurology*, Amlie-LeFond *et al.*³ assess current practices regarding the use of rtPA in children with acute arterial ischemic stroke. The children were all enrolled in the International Pediatric Stroke Study (IPSS), and the authors compared rtPA use in this cohort with evidence from published case reports.

Thrombolytic therapy has not been approved by the FDA for use in [children]

The IPSS, a multicenter, prospective pediatric ischemic stroke registry, includes 687 children (non-neonates) with arterial ischemic stroke enrolled from 30 centers in 10 countries between 2003 and 2007. Administration of rtPA was at the discretion of the local provider rather than part of a protocol. In some cases, thrombolytic therapy was administered at a community-based medical center before referral to an IPSS-affiliated center. 15 children received rtPA, representing 2% of children in the registry and 3% of children enrolled from US and Canadian centers. Interestingly, the children who received rtPA were all from the US ($n = 13$) or Canada ($n = 2$). Nine children received intravenous thrombolysis and six children underwent intra-arterial thrombolysis. Seven of the 15 children (47%) were treated outside the suggested time windows for thrombolysis in adults (3 h for intravenous rtPA and 6 h for intra-arterial rtPA at

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Competing interests

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the time of enrollment in the study). Median times to treatment were 3.3 h (range 2–52 h) for intravenous rtPA and 4.5 h (range 3.8–24 h) for intra-arterial rtPA. Two deaths occurred, both of which were unrelated to thrombolysis. Four asymptomatic and no symptomatic intracranial hemorrhages were recorded. The children enrolled in the IPSS and receiving rtPA were younger on average, were more likely to receive rtPA outside the established adult time frame, and tended to show poorer neurological outcomes than children in previously published case reports, although the absolute numbers were small and none reached statistical significance. The authors acknowledge that a publication bias exists, with the individual case studies tending to report short treatment intervals and positive outcomes. Their findings also emphasize the need for a safety and dose-finding study in children.

The Amlie-LeFond *et al.*³ and Janjua *et al.*² studies show that 1–3% of children with ischemic stroke are currently receiving thrombolytic therapy. For comparison, at many centers 5–10% of adult patients with stroke receive intravenous rtPA. Several issues limit the number of children who will be suitable candidates for thrombolysis. Children with stroke often present for medical care in a delayed fashion, owing to a lack of awareness of childhood stroke among parents and physicians.⁴ The incidence of ischemic stroke in children is much lower than in adults (~2 per 100,000 person-years in children⁵ versus 158 per 100,000 person-years in adults).⁶ Stroke mimics, such as postictal paralysis after a seizure or complicated migraine, are also more common in children than in adults, with these conditions accounting for 21% of cases seen by a pediatric brain-attack team.⁷ MRI confirmation of cerebral ischemia is important in children before thrombolysis is administered, and this can further delay the ‘door-to-needle’ time for this treatment. Certain stroke subtypes in children, such as cerebral arteriopathies, might be less responsive to rtPA than others. These factors all reduce the size of the pool of children who could be eligible for thrombolysis. More frustrating, however, is the fact that even when a child who seems to be a good candidate for thrombolytic therapy presents to a physician, no data are available on dosing, safety and efficacy. Whether the adult dose of 0.9 mg/kg body weight is a safe and effective dose in children is unclear. Of particular relevance in this context are reports of developmental variations in the coagulation and fibrinolytic systems, which might affect rtPA dosing.⁸

What recommendations can be made on the basis of the available data? When a clinician is faced with a child with possible acute arterial ischemic stroke, urgent consultation with and transfer to a center with pediatric stroke expertise should be strongly considered. The clinician should be aware that stroke mimics exist and that imaging confirmation of ischemic stroke is required in children (rather than simply a head CT scan to confirm the absence of hemorrhage, as is performed in adults before rtPA treatment). If thrombolytic therapy is considered, physicians should recognize that the outcome could be inferior to that seen in case reports. Physicians caring for children are accustomed to prescribing medications that have been insufficiently studied in this age group and are, therefore, being given off label. Considerable care should be taken, however, when adopting this approach for thrombolytic therapy. Encouragingly, the NIH Stroke Progress Review Group in 2006 identified clinical trials in pediatric stroke as a top priority, and specifically mentioned the need for safety data on rtPA use in children.⁹ Many challenges lie ahead but, hopefully, a dose-finding study for thrombolysis in pediatric stroke is on the horizon.¹⁰

MRI confirmation of cerebral ischemia is important in children before thrombolysis is administered...

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