Published in final edited form as:

J Child Neurol. 2011 September ; 26(9): 1121–1125. doi:10.1177/0883073811408091.

Potential Eligibility for Recombinant Tissue Plasminogen Activator Therapy in Children: A Population-Based Study

Laura L. Lehman, MD¹, Dawn O. Kleindorfer, MD², Jane C. Khoury, PhD³, Kathleen Alwell, BSN², Charles J. Moomaw, PhD², Brett M. Kissela, MD², and Pooja Khatri, MD, MSc²

¹Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

²Department of Neurology, University of Cincinnati College of Medicine, Cincinnati, OH, USA

³Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Abstract

Intravenous recombinant tissue plasminogen activator is an established therapy for adults with ischemic stroke. In this Greater Cincinnati/Northern Kentucky population-based study, 8% were eligible. However, no established therapy exists for children with acute ischemic stroke. Accordingly, investigators assessed rates of eligibility for recombinant tissue plasminogen activator therapy among children (<18 years of age) in the same population to aid planning of future clinical trials. The investigators identified 29 pediatric ischemic strokes during 3 separate study periods (1993-1994, 1999, and 2005) and determined potential eligibility for recombinant tissue plasminogen activator therapy based on 2007 American Heart Association guidelines for adults. Depending on how relative contraindications were considered, 1 to 3 cases (3%-10%) met eligibility criteria. On the basis of national pediatric stroke incidence rates extrapolated from our population, it is estimated that up to 178 children might be eligible for intravenous recombinant tissue plasminogen activator therapy annually in the United States. Thus, recruitment for clinical studies is likely to be challenging and requires a concerted multicenter effort.

Keywords

stroke; recombinant tissue plasminogen activator; cerebrovascular disease; clinical trials

The annual incidence of pediatric ischemic stroke in the United States is estimated to be between 0.58 and 3.6 per 100 000.¹⁻⁶ Pediatric ischemic stroke is associated with a 2% to 11% fatality rate and up to a 20% recurrence rate.⁷⁻¹⁰ Approximately 70% of children who survive an ischemic stroke have a lifelong neurological deficit.^{11,12}

© The Author(s) 2011

Corresponding Author: Laura Lehman, MD, MLC 2015, 3333 Burnett Avenue, Cincinnati, OH 45229, Laura.Lehman@cchmc.org.

Author Contributions

LLL: author of first draft of manuscript. DOK: project conception, funding support, critical review of manuscript. JCK: statistical analysis. KA and CJM: data collection and analysis, critical review of manuscript. BMK: funding support, critical review of manuscript. PK: project conception and design, data interpretation, drafting of manuscript, mentorship.

Declaration of Conflicting Interest

The authors declared a potential conflict of interest (eg, a financial relationship with the commercial organizations or products discussed in this article) as follows: Dr Kleindorfer is a member of the Genentech Speakers Bureau and a consultant for Boehringer-Ingelheim. The other authors have no conflict of interest to disclose.

Ethical Approval

Institutional Review Boards at all participating hospitals approved the study.

For adults (≥ 18 years of age) with acute ischemic stroke, intravenous recombinant tissue plasminogen activator is a US Food and Drug Administration–approved therapy that has been proved effective in reducing disability.^{13,14} There is no established therapy for children with acute ischemic strokes.

The literature regarding the use of recombinant tissue plasminogen activator in pediatric patients with acute ischemic stroke is limited to observational data.^{15–25} Among 2904 pediatric ischemic stroke admissions from 2003 to 2006 in the Nationwide Inpatient Sample, 46 (1.6%) cases received intravenous and/or intra-arterial thrombolysis, including 24 who received only intravenous recombinant tissue plasminogen activator.²⁶ Similarly, a multicenter, observational, prospective registry by the International Pediatric Stroke Study (IPSS) group reported use of thrombolysis in 15 (2.2%) cases among 687 ischemic strokes from 2003 to 2007.²⁷ For 7 of the 9 cases in the IPSS registry receiving intravenous-only recombinant tissue plasminogen activator, timing and dosing of intravenous recombinant tissue plasminogen activator varied substantially from the standard adult regimen of 0.9 mg/kg at less than 4.5 hours; 3 patients were treated at 5.5, 20, and 52 hours from symptom onset and 4 received alternate dosing. Only 7 of 15 (47%) thrombolysis cases in the International Pediatric Stroke Society had favorable outcomes, with mild or no deficits at 90 days.²⁸

American Heart Association pediatric stroke guidelines recommend against intravenous recombinant tissue plasminogen activator treatment for children with ischemic strokes outside a clinical trial, with the exception of older adolescents who otherwise meet adult eligibility criteria, for whom consensus is lacking.²⁸ A dose-escalation clinical trial of intravenous recombinant tissue plasminogen activator for the pediatric population has recently been proposed.²⁹

Currently, only 2% to 4% of the adult ischemic stroke population receives intravenous recombinant tissue plasminogen activator in the United States.³⁰ We examined eligibility rates for intravenous recombinant tissue plasminogen activator among acute ischemic stroke patients in our population-based 2005 epidemiological study and found that 8% should be eligible for intravenous recombinant tissue plasminogen activator.³¹ The primary contraindication for intravenous recombinant tissue plasminogen activator was delayed arrival to emergency departments. If time was not an exclusion criterion, up to 29% of adult ischemic stroke patients might have been eligible for intravenous recombinant tissue plasminogen activator.³²

For this analysis, we sought to determine the rate of eligibility for recombinant tissue plasminogen activator in a population-based cohort of pediatric stroke patients based on standard adult eligibility criteria.

Methods

We ascertained all strokes (ischemic and hemorrhagic) and transient ischemic attacks among residents of the Greater Cincinnati/Northern Kentucky region of 1.3 million people, as part of the National Institutes of Health–funded Greater Cincinnati/Northern Kentucky Stroke Study. The study collected stroke events over 3 one-year periods: July 1, 1993, to June 30, 1994, and calendar years 1999 and 2005. Study research nurses screened the medical records of all inpatients with primary or secondary stroke-related discharge diagnoses (*International Classification of Disease, Ninth Revision [ICH-9]* codes 430–436) from all acute-care hospitals in the study region. In addition, the research nurses screened codes 437 and 438 (which have been shown to have a very low yield for identifying strokes in adults) at Cincinnati Children’s Hospital to ensure complete capture of pediatric ischemic strokes.

Once potential cases were identified, a study nurse abstracted information from medical records, including demographics, stroke symptoms, time of symptom onset, and arrival in the emergency department. Study physicians reviewed every abstract, along with all available neuroimaging studies, to verify the occurrence of a stroke. Institutional review boards at all participating hospitals approved this study. Detailed methods are published elsewhere.³³⁻³⁵

To qualify as a case for the current analysis, a patient must have been younger than 18 years and must have had an acute ischemic stroke. For children 4 years and older, stroke severity was determined based by a validated method of estimating National Institutes of Health Stroke Scale score retrospectively, based on chart documentation.³⁶ Stroke onset was determined to be the time the child was noted to have any focal neurological deficit. This was typically based on parental report of when the child was last seen “normal.”

Pediatric stroke cases were retrospectively evaluated for eligibility to receive recombinant tissue plasminogen activator based on absolute and relative contraindications (Table 1) from the 2007 American Heart Association Guidelines for Early Management of Adults with Ischemic Stroke, with the exception of the relative contraindications of recent gastrointestinal/urinary hemorrhage, lumbar puncture, and arterial puncture, for which data were not available.³⁷ Cases were considered eligible for intravenous recombinant tissue plasminogen activator if they arrived within 3.5 hours from stroke onset to allow for treatment by 4.5 hours, per adult stroke guidelines.³⁸ The absolute criterion of less than 185/100 mm Hg for blood pressure in adults was used in this analysis, but this will likely need to be modified in a clinical trial of the pediatric population. Eligibility rates were additionally considered without using time as an exclusion criterion.

Results

During the 3 study periods within our population of 1.3 million, there were a total of 49 pediatric strokes: 14 during the 12-month period of 1993-1994, 21 during 1999 (2 recurrent events), and 14 during 2005 (2 recurrent events). Of the 49 events, 29 were ischemic strokes: 10 in 1993-1994, 11 in 1999, and 8 in 2005. The remaining cases were intracranial hemorrhages. The ischemic strokes included 7 neonates (< 28 days old), 4 infants (>28 days to <1 year), 11 children between 1 and 14 years, and 7 children between 15 and 17 years. Of the 29 ischemic stroke patients, 24 presented to the region's pediatric hospital, 3 presented to the region's university-based adult hospital, 1 was at a level 3 nursery at a community hospital when the stroke occurred, and 1 presented to a community hospital emergency department. Only 3 (10.3%) had documentation of assessment within 3.5 hours of stroke symptom onset. None received intravenous recombinant tissue plasminogen activator treatment.

Patients with absolute and relative contraindications are shown in Table 1. All 3 patients who presented within the 3.5-hour window had no absolute contraindication for recombinant tissue plasminogen activator besides age. However, 2 patients had relative contraindications to intravenous recombinant tissue plasminogen activator: seizures within 24 hours after presentation. Whether these seizures would have occurred prior to consideration of intravenous recombinant tissue plasminogen activator could not be determined from our data set. Ages of the 3 patients were 16 years, 15 years, and 348 days. Only the 16-year-old presented with no absolute or relative contraindication for recombinant tissue plasminogen activator.

Specific time of onset was recorded for only 6 of the 29 pediatric patients; 3 presented within 1 hour of symptom onset, and 3 presented more than 7 hours after onset (Figure 1). If

time were eliminated as an exclusion criterion, 20 (77%) patients would have had no absolute contraindications to recombinant tissue plasminogen activator, and 5 (17%) would have had no absolute or relative contraindications to recombinant tissue plasminogen activator (Table 1).

Discussion

Within our pediatric population, only 1 of 29 subjects (3%) with ischemic stroke would have been eligible for recombinant tissue plasminogen activator, according to adult criteria, over the 3 separate study periods. If time and relative contraindications were not used as exclusions, 20 (77%) of the 29 children would have been eligible for intravenous recombinant tissue plasminogen activator over the 3 study periods.

By the most liberal estimates (excluding time and relative contraindications), 178 children would meet eligibility to receive intravenous recombinant tissue plasminogen activator in the United States annually. This calculation is based on (1) an ischemic stroke incidence for children younger than 18 years of 2.4 per 100 000 per year (95% confidence interval, 1.7-3.6) in the United States after adjustment for age, sex, and race, and (2) a population estimate of 74 431 511 children younger than 18 years, including neonates, in the United States in 2010 from the Centers for Disease Control and Prevention Web site.³⁹

Population-based eligibility rates could be even lower than what our analysis suggests despite our liberal assumptions. We used adult eligibility criteria for this analysis, as pediatric eligibility criteria have not been determined. Pediatric criteria are likely to be more restrictive. For example, blood pressure thresholds for children will likely be lower than the adult threshold of less than 185/110 mm Hg. In addition, it may be appropriate to exclude neonates. We also had a lack of data regarding some of the relative contraindications that could lead to further exclusions for intravenous recombinant tissue plasminogen activator therapy in this group.

Although our estimate of eligibility for intravenous recombinant tissue plasminogen activator in the United States did not exclude patients with relative exclusions, further discussion of the specific relative contraindication of seizures is warranted. Seizures in the setting of stroke are much more common in pediatric stroke patients (59%) compared with adult stroke patients (3.1%), based on a study of seizures among pediatric strokes from the same Greater Cincinnati/Northern Kentucky cohort.³³ Precise timing of the seizures was not available, but it was assumed these occurred prior to determining eligibility for intravenous recombinant tissue plasminogen activator and they were treated as relative contraindications to intravenous recombinant tissue plasminogen activator treatment in this analysis.

However, if stroke had been confirmed by emergent imaging in these cases, these patients may have been eligible for intravenous recombinant tissue plasminogen activator despite this relative contraindication.

This analysis is limited by a very small sample size, which is likely to reflect the low incidence of the condition. Although the population-based design may have missed some cases given the retrospective chart review, due to either misclassified in-patient *ICH-9* codes, incomplete documentation in the medical record, underdiagnosis by clinicians, or presentations to outpatient settings, these limitations are unlikely to change our estimates in a meaningful way.⁴⁰ The population-based design allowed for more comprehensive ascertainment of true rates in a population, including adult hospitals, and with less bias than that of a referral center cohort.

Our analysis suggests that up to 170 cases might be eligible for a clinical trial of intravenous recombinant tissue plasminogen activator in the acute pediatric stroke population study in

the US population annually. Whether recombinant tissue plasminogen activator is safe and efficacious in this pediatric population needs further study, but recruitment will likely be very challenging because of limited availability of cases.

Acknowledgments

A portion of this work was presented as an oral abstract at the 2006 International Stroke Conference of the American Stroke Association.

Funding

The authors disclosed receipt of the following financial support for the research and/or authorship of this article: NIH/NINDS RO1 NS30678; NIH/NINDS K23 NS059843 (P.K.).

References

1. Earley CJ, Kittner SJ, Feaser BR, et al. Stroke in children and sickle-cell disease: Baltimore-Washington Cooperative Young Stroke Study. *Neurology*. 1998; 51:169–176. [PubMed: 9674798]
2. Schoenberg BS, Mellinger JF, Schoenberg DG. Cerebrovascular disease in infants and children: a study of incidence, clinical features, and survival. *Neurology*. 1978; 28:763–768. [PubMed: 567292]
3. Broderick J, Talbot GT, Prenger E, et al. Stroke in children within a major metropolitan area: the surprising importance of intracerebral hemorrhage. *J Child Neurol*. 1993; 8:250–255. [PubMed: 8409267]
4. Kleindorfer D, Khoury J, Kissela B, et al. Temporal trends in the incidence and case fatality of stroke in children and adolescents. *J Child Neurol*. 2006; 21:415–418. [PubMed: 16901448]
5. Fullerton HJ, Wu YW, Zhao S, Johnston SC. Risk of stroke in children: ethnic and gender disparities. *Neurology*. 2003; 61:189–194. [PubMed: 12874397]
6. Agrawal N, Johnston SC, Wu YW, et al. Imaging data reveal a higher pediatric stroke incidence than prior US estimates. *Stroke*. 2009; 40:3415–3421. [PubMed: 19762687]
7. Fullerton HJ, Wu YW, Sidney S, Johnston SC. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. *Pediatrics*. 2007; 119:495–501. [PubMed: 17332202]
8. Strater R, Becker S, von Eckardstein A, et al. Prospective assessment of risk factors for recurrent stroke during childhood—a 5-year follow-up study. *Lancet*. 2002; 360:1540–1545. [PubMed: 12443591]
9. Ganesan V, Prengler M, Wade A, Kirkham FJ. Clinical and radiological recurrence after childhood arterial ischemic stroke. *Circulation*. 2006; 114:2170–2177. [PubMed: 17075014]
10. Steinlin M, Pfister I, Pavlovic J, et al. The first three years of the Swiss Neuropaediatric Stroke Registry (SNSPR): a population-based study of incidence, symptoms and risk factors. *Neuropediatrics*. 2005; 36:90–97. [PubMed: 15822021]
11. Giroud M, Lemesle M, Gouyon JB, et al. Cerebrovascular disease in children under 16 years of age in the city of Dijon, France: a study of incidence and clinical features from 1985 to 1993. *J Clin Epidemiol*. 1995; 48:1343–1348. [PubMed: 7490597]
12. deVeber GA, MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. *J Child Neurol*. 2000; 15:316–324. [PubMed: 10830198]
13. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995; 333:1581–1587. [PubMed: 7477192]
14. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: Pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004; 363:768–774. [PubMed: 15016487]
15. Arnold M, Steinlin M, Baumann A, et al. Thrombolysis in childhood stroke: report of 2 cases and review of the literature. *Stroke*. 2009; 40:801–807. [PubMed: 19118242]

16. Jain SV, Morton LD. Ischemic stroke and excellent recovery after administration of intravenous tissue plasminogen activator. *Pediatr Neurol.* 2008; 38:126–129. [PubMed: 18206794]
17. Carlson MD, Leber S, Deveikis J, Silverstein FS. Successful use of rt-PA in pediatric stroke. *Neurology.* 2001; 57:157–158. [PubMed: 11445651]
18. Heil JW, Malinowski L, Rinderknecht A, et al. Use of intravenous tissue plasminogen activator in a 16-year-old patient with basilar occlusion. *J Child Neurol.* 2008; 23:1049–1053. [PubMed: 18827269]
19. Shuayto MI, Lopez JI, Greiner F. Administration of intravenous tissue plasminogen activator in a pediatric patient with acute ischemic stroke. *J Child Neurol.* 2006; 21:604–606. [PubMed: 16970853]
20. Thirumalai SS, Shubin RA. Successful treatment for stroke in a child using recombinant tissue plasminogen activator. *J Child Neurol.* 2000; 15:558. [PubMed: 10961797]
21. Ortiz GA, Koch S, Wallace DM, Lopez-Alberola R. Successful intravenous thrombolysis for acute stroke in a child. *J Child Neurol.* 2007; 22:749–752. [PubMed: 17641263]
22. Cannon BC, Kertesz NJ, Friedman RA, Fenrich AL. Use of tissue plasminogen activator in a stroke after radiofrequency ablation of a left-sided accessory pathway. *J Cardiovasc Electrophysiol.* 2001; 12:723–725. [PubMed: 11405408]
23. Cremer S, Berliner Y, Warren D, Jones AE. Successful treatment of pediatric stroke with recombinant tissue plasminogen activator (rt-PA): a case report and review of the literature. *CJEM.* 2008; 10:575–578. [PubMed: 19000355]
24. Noser EA, Felberg RA, Alexandrov AV. Thrombolytic therapy in an adolescent ischemic stroke. *J Child Neurol.* 2001; 16:286–288. [PubMed: 11332463]
25. Losurdo G, Giacchino R, Castagnola E, et al. Cerebrovascular disease and varicella in children. *Brain Dev.* 2006; 28:366–370. [PubMed: 16376509]
26. Janjua N, Nasar A, Lynch JK, Qureshi AI. Thrombolysis for ischemic stroke in children: data from the nationwide inpatient sample. *Stroke.* 2007; 38:1850–1854. [PubMed: 17431210]
27. Amlie-Lefond C, deVeber G, Chan AK, et al. Use of alteplase in childhood arterial ischaemic stroke: a multicentre, observational, cohort study. *Lancet Neurol.* 2009; 8:530–536. [PubMed: 19423401]
28. Roach ES, Golomb MR, Adams R, et al. Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. *Stroke.* 2008; 39:2644–2691. [PubMed: 18635845]
29. Whelan HT, Cook JD, Amlie-Lefond CM, et al. Practical model-based dose finding in early-phase clinical trials: optimizing tissue plasminogen activator dose for treatment of ischemic stroke in children. *Stroke.* 2008; 39:2627–2636. [PubMed: 18617665]
30. Kleindorfer D, Xu Y, Moomaw CJ, et al. US geographic distribution of rt-PA utilization by hospital for acute ischemic stroke. *Stroke.* 2009; 40:3580–3584. [PubMed: 19797701]
31. Kleindorfer D, Sandercock P, Khoury J, et al. Age-based eligibility for and treatment with rt-PA: a population-based estimate; Paper presented at: International Stroke Conference; San Antonio, TX. 2010; Feb.
32. Kleindorfer D, Kissela B, Schneider A, et al. Eligibility for recombinant tissue plasminogen activator in acute ischemic stroke: a population-based study. *Stroke.* 2004; 35:e27–e29. [PubMed: 14739423]
33. Broderick J, Brott T, Kothari R, et al. The greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever and total incidence rates of stroke among blacks. *Stroke.* 1998; 29:415–421. [PubMed: 9472883]
34. Broderick JP, Brott T, Tomsick T, et al. The risk of subarachnoid and intracerebral hemorrhages in blacks as compared with whites. *N Engl J Med.* 1992; 326:733–736. [PubMed: 1738378]
35. Chadehumbe MA, Khatri P, Khoury JC, et al. Seizures are common in the acute setting of childhood stroke: a population-based study. *J Child Neurol.* 2009; 24:9–12. [PubMed: 18923086]
36. Williams LS, Yilmaz EY, Lopez-Yunez AM. Retrospective assessment of initial stroke severity with the NIH Stroke Scale. *Stroke.* 2000; 31:858–862. [PubMed: 10753988]

37. Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Inter-disciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007; 38:1655–1711. [PubMed: 17431204]
38. Bluhmki E, Chamorro A, Davalos A, et al. Stroke treatment with alteplase given 3.0–4.5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial. *Lancet Neurol*. 2009; 8:1095–1102. [PubMed: 19850525]
39. Centers for Disease Control and Prevention. CDC Wonder on the Web. Population projections, United States, 2004–2030, by state, age and sex. Available at: <http://wonder.cdc.gov/population-projections.html>
40. Golomb MR, Garg BP, Saha C, Williams LS. Accuracy and yield of ICD-9 codes for identifying children with ischemic stroke. *Neurology*. 2006; 67:2053–2055. [PubMed: 17159120]

Figure 1.
Time from Onset to Emergency Department Arrival of Pediatric Ischemic Stroke Patients.

Table 1

Absolute and Relative Contraindication for Recombinant Tissue Plasminogen Activator, n (%)

	3.5-h Emergency Department Arrival (n = 3)	>3.5-h or Unknown Emergency Department Arrival (n = 26)
Absolute contraindications		
History of intracranial hemorrhage, subarachnoid hemorrhage, or intraventricular hemorrhage	0	0
Blood pressure >185/110	0	0
International normalized ratio >1.6	0	1 (3.8)
Partial thromboplastin time >40 s	0	1 (3.8)
Platelets <100 000	0	3 (11.5)
Stroke, intracranial surgery, or head trauma <3 months	0	1 (3.8)
Aneurysm, AVM, or brain tumor	0	1 (3.8)
Total eligible (based on absolute contraindications)	3 (100)	20 (76.9)
Relative contraindications		
Seizure	2 (66.7)	15 (57.7)
Glucose <50 or >400	0	1 (3.8)
NIHSS < ^a 5	0	9 (34.6)
Major trauma/surgery <15 d	0	0
Recent myocardial infarction or post-myocardial infarction pericarditis	0	0
Total eligible (based on absolute and relative contraindications)	1 (33.3)	4 (15.4)

Abbreviations: AVM, arteriovenous malformation; NIHSS, National Institutes of Health Stroke Scale.

^aNIHSS was determined based on retrospective chart-based review and included only subjects 4 years old or older (ie, 15 of 29 cases).