Cerebral Venous Thrombosis

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INTRODUCTION

Background

Thrombosis of the venous channels in the brain is an uncommon cause of cerebral infarction relative to arterial disease but is an important consideration because of its potential morbidity. Venous thrombosis may occur with headache and cranial nerve palsies. Newer imaging procedures have led to easier recognition of venous sinus thrombosis, offering the opportunity for early therapeutic measures. Venous thrombosis also may be associated with other medical complications that require therapeutic intervention.

Pathophysiology
Knowledge of the anatomy of the venous system is essential in evaluating patients with venous thrombosis, since symptoms associated with the condition are related to the area of thrombosis. Cerebral infarction may occur with cortical vein or sagittal sinus thrombosis secondary to tissue congestion with obstruction. Lateral sinus thrombosis may be associated with headache and a pseudotumor cerebri–like picture. Extension into the jugular bulb may cause jugular foramen syndrome; cranial nerve palsies may be seen in cavernous sinus thrombosis as a compressive phenomenon. Cerebral hemorrhage also may be a presenting feature in patients with venous sinus thrombosis.

**Frequency**

**International**

Incidence of cerebral venous thrombosis (CVT) is difficult to determine. Generally, it is believed to be an uncommon cause of stroke. However, with the advent of newer imaging techniques, the reported incidence is likely to increase as less severe cases are found. In 1973, Towbin reported CVT in 9% of 182 autopsies. In 1995, Daif reported a frequency in Saudi Arabia of 7 cases per 100,000 hospital patients. The ratio of venous to arterial strokes has been found to be 1:62.5.

**Mortality/Morbidity**

Mortality in untreated cases of venous thrombosis has been reported to range from 13.8-48%; this high mortality rate may be a reflection of clinical severity at entrance into the study. Between 25% and 30% of patients have full recovery.

More recently, a Portuguese study group prospectively analyzed 91 consecutively admitted patients from 1995 to 1998 over a mean 1-year follow-up interval (Ferro, 2002). Of the patients analyzed, 7% died in the acute phase, 1% died during the one year follow-up, 82% recovered completely, and 1% were dependent; 59% developed thrombotic events during the follow-up, 10% had seizures, 11% complained of severe headaches, and 1 patient experienced severe visual loss.

In 2003, Buccino et al found a good overall outcome in their reinvestigation of a series of 34 patients with confirmed cerebral venous thrombosis. However, 10 patients (30%) had episodic headaches, 3 patients (8.8%) had seizures, 4 patients (11.7%) had pyramidal signs, and 2 (5.9%) had visual deficits. Mild nonfluent aphasia was seen in 3 patients. Working memory deficit and depression of mood were seen in 6 patients (17.6%).

**Race**

No racial predilection has been observed.
Sex

CVT is believed to be more common in women than men. In a series of 110 cases, Ameri and Bousser found a female-to-male ratio of 1.29:1 (Ameri, 1992).

Age

In 1992, Ameri and Bousser reported a uniform age distribution in men with CVT, while 61% of women with CVT were aged 20-35 years. This may be related to pregnancy or the use of oral contraceptives.

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History

- Patients may present with headache. Although thunderclap headache usually indicates subarachnoid hemorrhage (SAH), it also may be seen in sinus thrombosis.
- SAH has been described as the presenting event with CVT. CVT should be considered in the workup of SAH, especially when the basilar cisterns are not involved (Oppenheim, 2005).
- Nausea and vomiting may be associated.
- Patients with lateral sinus thrombosis may present with a pseudotumor cerebri–like syndrome. Using a technique called auto-triggered elliptic-centric-ordered 3-dimensional gadolinium-enhanced MR venography,
Farb et al found that 27 of 29 patients with idiopathic intracranial hypertension had bilateral sinovenous stenosis; this was seen in only 4 of 59 control subjects (Farb, 2003).

- Patients may have seizures that can be recurrent.
- Patients may have a decreased level of consciousness that progresses to coma.
- Focal neurological deficit may occur depending on the area involved.
  - Hemiparesis may occur, and in some cases of sagittal sinus thrombosis, weakness in the lower extremity. This also may develop as bilateral lower extremity involvement.
  - Aphasia, ataxia, dizziness, chorea, and hemianopia all have been described.
- Cranial nerve syndromes are seen with venous sinus thrombosis. These include the following:
  - Vestibular neuronopathy
  - Pulsatile tinnitus
  - Unilateral deafness
  - Double vision
  - Facial weakness
  - Obscuration of vision

**Physical**

- Mental status may be quite variable, with patients showing no change in alertness, developing mild confusion, or progressing to coma.
- Cranial nerve findings may include papilledema, hemianopia, oculomotor and abducens palsies, facial weakness, and deafness. If the thrombosis extends to the jugular vein, the patient may develop involvement of cranial nerves IX, X, XI, and XII with the jugular foramen syndrome.
- Thrombosis of the superior sagittal (longitudinal) sinus may present with unilateral paralysis that then extends to the other side secondary to extension of the clot into the cerebral veins. Because of the location, this may present as a unilateral lower extremity weakness or paraplegia.
- Cavernous sinus thrombosis with obstruction of the ophthalmic veins may be associated with proptosis and ipsilateral periorbital edema. Retinal hemorrhages and papilledema may be present. Paralysis of extraocular movements, ptosis, and decreased sensation in the first division of the trigeminal nerve often are observed.
- Although unusual, cortical vein thrombosis may be seen in the absence of dural sinus involvement. These cases are associated with varied focal deficits including aphasia, hemiparesis, hemisensory loss, and hemianopia.

**Causes**
Many causative conditions have been described in CVT. These may be seen alone or in combination. For example, the prothrombin gene mutation in association with oral contraceptive use raises the odds ratio for developing CVT.

- Infection may occur by extension from the paranasal sinuses. These cases also may be associated with subdural empyema. Bacterial meningitis as a coexistent condition should be considered in these cases. Frontal sinuses are the most common source of infection, with spread through the emissary veins between the posterior sinus mucosa and the meninges. Rarely, sphenoid sinusitis may be associated with cavernous sinus thrombosis. Multiple organisms are to be considered, *Staphylococcus aureus* being the most common. In chronic infections, gram-negative organisms and fungi such as *Aspergillus* species may be found.

- Trauma may be an etiologic event. Cerebral sinus thrombosis easily may be overlooked in cases of minor head trauma. Neurosurgical procedures such as dural taps and infusions into the internal jugular vein also have been implicated.

- Many medical conditions have been associated with venous sinus thrombosis.
  - Pregnancy and puerperium are important considerations in women of childbearing age.
  - Inflammatory bowel diseases such as Crohn disease and ulcerative colitis are described as risk factors for venous thrombosis. Corticosteroids used in treatment of these conditions may play a causative role.
  - Hypercoagulable states associated with the antiphospholipid syndrome, protein S and C deficiencies, antithrombin III deficiency, lupus anticoagulant, and the Leiden factor V mutation may result in CVT. Pregnancy also is associated with a hypercoagulable tendency.
  - Hematologic conditions, including paroxysmal nocturnal hemoglobinuria, thrombotic thrombocytopenic purpura, sickle cell disease, and polycythemia, are to be considered. Malignancies may be associated with hypercoagulable states and therefore may be risk factors.
  - Collagen-vascular diseases such as systemic lupus erythematosus, Wegener granulomatosis, and Behçet syndrome have been reported to be associated with CVT.
  - Nephrotic syndrome, dehydration, hepatic cirrhosis, and sarcoidosis all have been described as increasing the risk of CVT.

- Several medications are reported to increase the risk of CVT. Among these are oral contraceptives, including the third-generation formulations; corticosteroids; epsilon-aminocaproic acid; and L-asparaginase. Heparin
therapy has been reported to produce thrombotic thrombocytopenia with associated venous sinus thrombosis.

DIFFERENTIALS

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Acute Stroke Management
Blood Dyscrasias and Stroke
Cavernous Sinus Syndromes
Cerebral Venous Thrombosis
Head Injury
HIV-1 Associated Opportunistic Infections: Cytomegalovirus Encephalitis
Intracranial Epidural Abscess
Lumbar Puncture (CSF Examination)
Pseudotumor Cerebri
Sarcoidosis and Neuropathy
Staphylococcal Meningitis
Status Epilepticus
Stroke Anticoagulation and Prophylaxis
Subdural Empyema
Systemic Lupus Erythematosus

Other Problems to be Considered

Abducens (VI) nerve palsy

WORKUP
Lab Studies

- Clinical laboratory studies are useful for determining the possible causes of CVT. Diagnosis of the condition is made on the basis of clinical presentation and imaging studies.
- CBC count is performed to look for polycythemia as an etiologic factor. Decreased platelet count would support thrombotic thrombocytopenic purpura; leukocytosis might be seen in sepsis. In addition, if heparin is used as treatment, platelet counts should be monitored for thrombocytopenia.
- Antiphospholipid and anticardiolipin antibodies should be obtained to evaluate for antiphospholipid syndrome. Other tests that may indicate hypercoagulable states include protein S, protein C, antithrombin III, lupus anticoagulant, and Leiden factor V mutation. These evaluations should not be made while the patient is on anticoagulant therapy.
- Sickle cell preparation or hemoglobin electrophoresis should be obtained in individuals of African decent.
- Erythrocyte sedimentation rate and antinuclear antibody should be performed for screening of systemic lupus erythematosus, Wegener granulomatosis, and temporal arteritis. If elevated, further evaluation including complement levels, anti-DNA antibodies, and neutrophil cytoplasmic antibodies (ANCA) could be considered.
- Urine protein should be checked and, if elevated, nephrotic syndrome considered.
- Liver function studies should be performed to rule out cirrhosis.
- D-dimer values may be beneficial in screening patients who present in the emergency department for headache evaluation.
In a study of 18 patients with CVT, Tardy et al reported that D-dimer levels less than 500 ng/mL had a negative predictive value for ruling out the diagnosis in patients with acute headache (Tardy, 2002).

In a prospective study of 54 consecutive patients with headache suggestive of CVT, Lalive found that 12 had CVT and, of those, 10 had D-dimer levels greater than 500 ng/mL (Lalive, 2003). The 2 patients with confirmed CVT and a D-dimer level less than 500 ng/mL had a history of chronic headache lasting longer than 30 days.

Kosinski et al (2004) prospectively studied 343 patients with symptoms suggesting cerebral sinus thrombosis. The diagnosis was confirmed in 35, with 34 of these patients showing elevated D-dimer levels greater than 500 mcg/L. Of the 308 patients not having CVT, 27 had positive values. Sensitivity was 97.1%, with a negative predictive value of 99.6%. Specificity was 91.2%, with a positive predictive value of 55.7%. D-dimers were positively correlated with the extent of thrombosis and negatively correlated with duration of symptoms. This test does not establish the diagnosis of CVT, and more definitive studies, such as MR venography (MRV), are necessary. Likewise, if a high suspicion for CVT exists, the test does not definitely exclude the diagnosis but makes the presence of CVT very unlikely.

**Imaging Studies**

- MRI
  - MRI shows the pattern of an infarct that does not follow the distribution of an expected arterial occlusion. It may show absence of flow void in the normal venous channels.
  - MRV is an excellent method of visualizing the dural venous sinuses and larger cerebral veins.
  - Single-slice phase-contrast angiography (SSPCA) takes less than 30 seconds and provides rapid and reliable information. Many neurologists now consider it to be the procedure of choice in diagnosing CVT. In a study of 21 patients, Adams demonstrated a specificity and sensitivity of 100% for SSPCA when compared to alternative imaging techniques (Adams, 1999).
  - However, Ayanzen described transverse sinus flow gaps in 31% of patients with normal MRI findings; 90% of these were in the nondominant transverse sinus, and 10% in the codominant sinuses. None was seen in the dominant sinus (Ayanzen, 2000). These should not be mistaken for thrombosis.
  - Mas et al describe increased intraluminal signal on all planes and with all pulse sequences in patients with lateral sinus thrombosis.
compared with frank asymmetry in size of the lateral sinus without any abnormal signal in the course of the sinus (Mas, 1990).

- **CT**
  - CT is an important imaging technique, as it is often the first imaging study obtained. It may show evidence of infarction that does not correspond to an arterial distribution. However, in the absence of a hemorrhagic component, demonstration of the infarct may be delayed up to 48-72 hours. It is also useful in ruling out other conditions such as neoplasm and in evaluating coexistent lesions such as subdural empyema. CT of the sinuses is useful in evaluating sinusitis; CT of the mastoids may be helpful in lateral sinus thrombosis.
  - Empty delta sign appears on contrast scans as enhancement of the collateral veins in the superior sagittal sinus (SSS) walls surrounding a nonenhanced thrombus in the sinus. However, the sign is frequently absent. Early division of the SSS can give a false delta sign. The dense triangle sign formed by fresh coagulated blood in the SSS and the cord sign representing thrombosed cortical vein are extremely rare.
  - CT angiography has also been used to visualize the cerebral venous system. Ozsvath et al compared CT and MR projection in the identification of cerebral veins and thrombosis. CT venography was superior to MR in identification of cerebral veins and dural sinuses. CT was equivalent to MR in identification of dural sinus thrombosis and therefore is a viable alternative to MR venography in the examination of patients with suspected dural sinus thrombosis. The maximum-intensity-projection technique used, however, did not allow direct visualization of the thrombus by either CT or MR technique.

- **Contrast studies**
  - Carotid arteriography with delayed filming technique to visualize the venous system was the procedure of choice in the diagnosis of venous thrombosis prior to the advent of MRV. It is an invasive procedure and is therefore associated with a small risk.
  - If MR studies are not diagnostic, conventional angiography should be considered.
  - Direct venography can be performed by passing a catheter from the jugular vein into the transverse sinus with injection outlining the venous sinuses.

**Other Tests**
• EEG may be normal, show mild generalized slowing, or show focal abnormalities if a unilateral infarct occurs. It is helpful in evaluating a seizure focus.

Procedures

• Lumbar puncture is helpful in evaluating for meningitis as an associated infectious process. A large unilateral hemispheric lesion or posterior fossa lesion demonstrated on CT scan or MRI is a contraindication to the procedure. In the past, compression of the jugular vein unilaterally with pressure measurement has been utilized. Pressure may be elevated if thrombosis of the contralateral transverse sinus is present. However, collateral circulation or incomplete compression of the jugular vein may yield a false-negative result. Elevation of the intracranial venous pressure is a concern, as it may precipitate herniation. As the maneuver adds little to the diagnosis, it usually is not performed.

TREATMENT

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Medical Care

Medical management of the patient with CVT is similar to that of patients with arterial stroke as far as stabilizing the patient is concerned.

• Patients with altered mental status or hemiplegia should be given nothing by mouth to prevent aspiration. Intravenous fluids should not be hypotonic solutions. Normal saline is recommended at a rate of approximately 1000
mL in 24 hours. To decrease intracranial pressure, the head should be elevated 30-40° at all times. In the treatment of stroke patients, supplemental oxygen has not been shown to be beneficial unless level of consciousness is decreased.

- **Seizures** should be treated with appropriate anticonvulsants. Fosphenytoin is recommended for treatment of seizures in those patients who require a parenteral formulation. Alternatively, phenobarbital or sodium valproate injection may be utilized if the patient has allergy to phenytoin. Diazepam or lorazepam may be used to treat status epilepticus, but the patient also should be given an anticonvulsant with a longer duration of action to prevent recurrent seizures.

- **Specific therapy for CVT involves anticoagulation or thrombolytic therapy.** Use of anticoagulation in CVT has been a subject of some debate among neurologists. Concern has been expressed over the possibility of increasing hemorrhage in patients treated in this manner. Studies by De Bruijn and Stam in 1999 and by Einhaupl in 1991 indicated that anticoagulation could be used safely in this condition. The question of effectiveness of anticoagulation is not clear, but most articles tend to point toward improved outcome with utilization of anticoagulation.
  
  - Thrombolytic therapy has been described in several case reports as beneficial in cases of CVT. These patients were treated with infusion of a thrombolytic agent into the dural venous sinus utilizing microcatheter technique. This treatment at present is limited to specialized centers but should be considered for patients with significant deficit.
  
  - A recent report describes the use of a rheolytic catheter device in a patient who had not responded to microcatheter instillation of urokinase. The rheolytic catheter was designed for use in the coronary circulation and delivers 6 high-velocity saline jets through a halo device at the tip of the catheter. This leads to a Bernoulli effect that breaks up the thrombus. In addition, the particulate debris is directed into an effluent lumen for collection into a disposable bag. The catheter was advanced into the sagittal sinus, resulting in restoration of venous flow and reduction of intracranial pressure.

**Surgical Care**

In cases of severe neurological deterioration, open thrombectomy and local thrombolytic therapy have been described as beneficial. Patients selected for these procedures have progressed despite adequate anticoagulation and intensive medical care. Ekseth described 3 such patients who all returned to normal lives following this procedure (Ekseth, 1998).

**Consultations**
• Consultation with a neurosurgeon is indicated in patients with subdural empyema or brain abscess. Consultation should also be considered for patients who have severe deterioration despite aggressive medical management.
• Consultation with an infectious disease specialist is to be considered for patients with CVT who have associated infection such as meningitis or sinusitis.
• Consultation with an otolaryngologist may be helpful in patients with associated sinusitis.

Management of Acquired Hemophilia in the Emergency Department

eMedicine invites you to participate in a series of free, interactive, case-based activities on the treatment of acquired hemophilia.

A 54-Year-Old Woman with Rheumatoid Arthritis, Bruising, Swelling, and Pain
Barbara M—, a 54-year-old white woman, presents to the emergency department with complaints of fatigue, bruising, and increasing pain and swelling in her left posterior thigh, hip, and buttock. (This activity is approved for AMA PRA Category 1 Credit™.)

MEDICATION

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Heparin should be considered seriously in the management of CVT. Conversion to warfarin as maintenance therapy is then suggested. Subcutaneous low-molecular-weight heparin (Lovenox) also has been used in patients with venous sinus thrombosis.

Thrombolytic therapy may be useful, but all studies so far describe its use only with local instillation by microcatheter or direct instillation at the time of surgical thrombectomy.

**Drug Category: Anticoagulants**

These medications are used to prevent propagation of the clot to more extensive areas of the cerebral venous system. Studies indicate a tendency toward better outcome in patients treated with anticoagulant therapy than in those who are not treated with anticoagulants. In Einhaupl's study, even patients with cerebral hemorrhage appeared to benefit from anticoagulation.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>Increases the action of antithrombin III, leading to inactivation of coagulation enzymes thrombin, factor Xa, and factor IXa. Thrombin is the most sensitive to inactivation by heparin. Because heparin is not absorbed from the GI tract, it must be given parenterally. When given IV, effect is immediate. Metabolism of heparin is complex; rapid zero-order metabolism is followed by slower first-order renal clearance. Zero-order process is saturable, leading to an increase in half-life from 30-150 min as dose increased. Weight-based protocol now often used for dosing. When choosing this therapy, risks of its contraindications must be weighed against potential benefits.</td>
</tr>
</tbody>
</table>

| Adult Dose | Initial infusion: 18 U/kg/h IV; aPTT checked in 6 h and q6h after any dosage change, as well as every am; adjust dose according to following parameters aPTT = <1.2 times control: 80 U/kg |

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<table>
<thead>
<tr>
<th><strong>Pediatric Dose</strong></th>
<th>Not established</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contraindications</strong></td>
<td>Documented hypersensitivity, aneurysm, active or recent bleeding, coagulopathy, endocarditis, hemophilia, hepatic disease, hypertension, inflammatory bowel disease, lumbar puncture/spinal anesthesia, sulfite hypersensitivity, surgery, thrombocytopenia</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>Digoxin, nicotine, tetracycline, and antihistamines may decrease effects; NSAIDs, aspirin, dextran, dipyridamole, and hydroxychloroquine may increase toxicity</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>Monitor platelet count for development of thrombocytopenia; severe hyperkalemia may occur with concomitant use of ACE inhibitors; increased bleeding risk occurs with many drugs, including platelet inhibitors, NSAIDs, valproic acid, Ginkgo biloba, and probenecid</td>
</tr>
<tr>
<td><strong>Drug Name</strong></td>
<td>Warfarin (Coumadin)</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>Interferes with action of vitamin K, a cofactor essential for converting precursor proteins into factors II, VII, IX, and X. Does not affect activity of coagulation factors synthesized prior to exposure to warfarin. Depletion of these mature factors by normal metabolism must occur before therapeutic effects of newly synthesized factors can be seen, thus may take several days to become</td>
</tr>
</tbody>
</table>
Effective. Dose influenced by differences in absorption, metabolism, and hemostatic responses to given concentrations; dose must be monitored closely by following PT and INR. Higher initial doses do not appear to improve time required to achieve therapeutic levels but do increase bleeding risk. Expert opinion is that warfarin treatment should be maintained for 3-6 mo, but no randomized, placebo-controlled trials have addressed this issue.

<table>
<thead>
<tr>
<th>Adult Dose</th>
<th>Initial: 5 mg PO qd; adjust dose by monitoring INR (target, 2.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Dose</td>
<td>Initial: 0.2 mg/kg PO up to 10 mg Maintenance: 0.1 mg/kg/d; INR must be monitored to determine maintenance dose</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity, alcoholism, aneurysm, bleeding, breastfeeding, endocarditis, pregnancy, hemophilia, lumbar puncture, thrombocytopenia, hypertension, leukemia, polycythemia vera, intracranial bleeding, vitamin C deficiency, vitamin K deficiency</td>
</tr>
<tr>
<td>Interactions</td>
<td>Monitor INR whenever a medication is added or discontinued; drugs that may decrease anticoagulant effects include griseofulvin, carbamazepine, glutethimide, estrogens, nafcillin, phenytoin, rifampin, barbiturates, cholestyramine, colestipol, vitamin K, spironolactone, oral contraceptives, and sucralfate; medications that may increase anticoagulant effects include oral antibiotics, phenylbutazone, salicylates, sulfonamides, chloral hydrate, clofibrate, diazoxide, anabolic steroids, ketoconazole, ethacrynic acid, miconazole, nalidixic acid, sulfonylureas, allopurinol, chloramphenicol, cimetidine, disulfiram, metronidazole, phenylbutazone,</td>
</tr>
</tbody>
</table>
## Drug Category: Thrombolytics

These agents cause lysis of the clot. All studies concerning the use of these agents in CVT involve either direct instillation into the sinus at the time of surgery or the use of microcatheters to reach the venous sinus.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Description</th>
<th>Adult Dose</th>
<th>Pediatric Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteplase</td>
<td>Biosynthetic form of human tissue plasminogen activator. Tissue plasminogen activator exerts effect on fibrinolytic system to convert plasminogen to plasmin. Plasmin degrades fibrin, fibrinogen, and procoagulant factors V and VIII. Not given as IV infusion to treat CVT. Refer patient to facility with expertise to perform venous sinus catheterization.</td>
<td>1 mg/cm infused via venous sinus catheter throughout clot, then 1-2 mg/h</td>
<td>Not established</td>
</tr>
</tbody>
</table>

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### Precautions

May cause uncontrolled bleeding and should not be used in conditions in which bleeding would be difficult to control, leading to a more catastrophic outcome; medications that inhibit platelet function should be avoided, including aspirin, NSAIDs, and valproic acid; patients with protein S or C deficiency may become transiently hypercoagulable (anticoagulate patient with heparin and then convert to warfarin); do not switch brands after achieving therapeutic response; caution in active tuberculosis or diabetes; patients with protein C or S deficiency are at risk of developing skin necrosis.

### Pregnancy

X - Contraindicated in pregnancy

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**Phenytoin, propoxyphene, sulfonamides, gemfibrozil, acetaminophen, and sulindac; supplements such as ginger and Ginkgo biloba should be avoided; green leafy vegetables have high levels of vitamin K, which may decrease INR**
### Contraindications
Documented hypersensitivity, aneurysm, arteriovenous malformation, bleeding, coagulopathy, endocarditis, diabetic retinopathy, mitral stenosis, recent surgery, pregnancy, breastfeeding

### Interactions
Drugs that alter platelet function (e.g., aspirin, dipyridamole, abciximab) may increase risk of bleeding prior to, during, or after alteplase therapy; may give heparin with and after alteplase infusions to reduce risk of rethrombosis; either heparin or alteplase may cause bleeding complications

### Pregnancy
C - Safety for use during pregnancy has not been established.

### Precautions
Monitor for bleeding, especially at arterial puncture sites, with coadministration of vitamin K antagonists; control and monitor BP frequently during and following alteplase administration (when managing acute ischemic stroke); do not use >0.9 mg/kg to manage acute ischemic stroke; doses >0.9 mg/kg may cause intracranial hemorrhage

### Drug Name
Urokinase (Abbokinase)

### Description
Produced by kidney, converts plasminogen to plasmin by cleaving arginine-valine bond in plasminogen. Degradation products of fibrin and fibrinogen exert clinically significant anticoagulant effect. Erythrocyte aggregation and plasma viscosity also are reported to decrease. Given in CVT by catheterization of venous sinus or by direct instillation at surgery during thrombectomy.

### Adult Dose
250,000 U/h instilled directly or via venous sinus catheter; additional doses of 50,000 U; total dose 1,000,000 U over 2 h

### Pediatric Dose
Not established
<table>
<thead>
<tr>
<th><strong>Contraindications</strong></th>
<th>Documented hypersensitivity, aneurysm, arteriovenous malformation, bleeding, coagulopathy, endocarditis, diabetic retinopathy, mitral stenosis, recent surgery, pregnancy, breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interactions</strong></td>
<td>Effects increased with coadministration of aminocaproic acid, anticoagulants, antineoplastic agents, antithymocyte globulin, cefamandole, cefoperazone, Ginkgo biloba, NSAIDs, platelet inhibitors, porfimer, strontium-89 chloride, sulfonpyrazone, tranexamic acid, valproic acid</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>B - Usually safe but benefits must outweigh the risks.</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>Caution in patients receiving IM administration of medications or with severe hypertension or trauma or surgery in previous 10 d; do not measure BP in lower extremities, because may dislodge DVT; monitor therapy by performing PT, aPTT, TT, or fibrinogen approximately 4 h after initiation of therapy</td>
</tr>
<tr>
<td><strong>Drug Name</strong></td>
<td>Streptokinase (Kabikinase, Streptase)</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>Facilitates thrombolysis through formation of an activator complex with plasminogen. Indirectly cleaves arginine-valine bond in plasminogen, forming plasmin. Plasmin degrades fibrin, fibrinogen, and procoagulant factors V and VIII. Degradation products of fibrin and fibrinogen have significant anticoagulant effect.</td>
</tr>
<tr>
<td><strong>Adult Dose</strong></td>
<td>Instilled directly or via venous sinus catheter</td>
</tr>
<tr>
<td><strong>Pediatric Dose</strong></td>
<td>Only anecdotal reports describe use in children, and that in arterial occlusion; doses used were as follows Loading dose: 1000-3000 IU/kg; followed by infusion of 1000-1500 IU/kg/h; in CVT, administered by direct infusion via catheter</td>
</tr>
</tbody>
</table>
### Contraindications
Documented hypersensitivity, aneurysm, arteriovenous malformation, bleeding, coagulopathy, endocarditis, diabetic retinopathy, mitral stenosis, recent surgery, pregnancy, breastfeeding

### Interactions
Effects are increased with coadministration of aminocaproic acid, anticoagulants, antineoplastic agents, antithymocyte globulin, cefamandole, cefoperazone, Ginkgo biloba, NSAIDs, platelet inhibitors, porfimer, strontium-89 chloride, sulfinpyrazone, tranexamic acid, valproic acid

### Pregnancy
C - Safety for use during pregnancy has not been established.

### Precautions
Caution in severe hypertension, IM administration of medications, trauma or surgery in previous 10 d; measure hematocrit, platelet count, aPTT, TT, PT, or fibrinogen levels before therapy is implemented; either TT or aPTT should be <2 times the normal control value following infusion of streptokinase and before (re)instituting heparin; do not take BP in lower extremities, as possible DVT may be dislodged; PT, aPTT, TT, or fibrinogen should be monitored 4 h after initiation of therapy; in addition to bleeding complications inherent in thrombolytic agents, repeated administration of streptokinase can result in tolerance as well as hypersensitivity

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**FOLLOW-UP**

Section 8 of 11 [Back Top Next]

- Authors and Editors
- Introduction
- Clinical
Prognosis

Smith compared outcomes of patients treated with heparin and local infusion of urokinase with those of patients who received no treatment. Twelve patients received treatment and 21 patients received no treatment. Results are tabulated below.

CVT Patients Treated with Heparin and Local Infusion of Urokinase vs Nontreated Group

<table>
<thead>
<tr>
<th></th>
<th>Treated Group, % (n = 12)</th>
<th>Nontreated Group, % (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full recovery</td>
<td>62.5</td>
<td>29</td>
</tr>
<tr>
<td>Mild disability</td>
<td>12.5</td>
<td>13</td>
</tr>
<tr>
<td>Severe disability</td>
<td>12.5</td>
<td>9.6</td>
</tr>
<tr>
<td>Fatal outcome</td>
<td>12.5</td>
<td>48</td>
</tr>
</tbody>
</table>

**MISCELLANEOUS**

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Medical/Legal Pitfalls

Potential medical/legal pitfalls involve failure to properly diagnose associated conditions. Following are some examples:

- Failure to aggressively treat frontal sinusitis leading to subdural empyema or CVT
- Failure to consider MRI or MRV in patients with pseudotumor cerebri to look for lateral sinus thrombosis (unless other etiology is found)
- Failure to consider CVT in patients with thunderclap headache; since such headache is not limited to SAH and may be seen with CVT, lack of evidence of SAH should prompt MRV
- Failure to check patients with CVT for associated medical conditions such as hypercoagulable states, nephrotic syndrome, pregnancy, liver disease, and inflammatory bowel disease
- Failure to consider medications that might lead to CVT, such as steroids and oral contraceptives
- Failure to distinguish normal anatomic gaps in the dural sinuses from thrombosis on MRV

MULTIMEDIA

Section 10 of 11
Media file 1: Case 1: Left lateral sinus thrombosis demonstrated on MR venography. This 42-year-old woman presented with sudden onset of headache. Physical examination revealed no neurological abnormalities.

Media file 2: Case 1: One week after treatment with heparin, the MR venogram of the patient described in Image 1 displayed increased flow in the left lateral sinus consistent with early recanalization of the sinus; headache had resolved at this point.

Media file 3: Magnetic resonance venogram - axial view; A = lateral (transverse) sinus; B = sigmoid sinus; C = confluence of sinuses; and D = superior sagittal sinus.
Media file 4: Magnetic resonance venogram - sagittal view; A = lateral (transverse) sinus; C = confluence of sinuses; D = superior sagittal sinus; and E = straight sinus.

Media file 5: Case 2: CT scan demonstrates a left posterior temporal hematoma in a 38-year-old woman on oral contraceptives (the only identified risk factor).

Media file 6: Case 2: Contrast-enhanced MRI showing lack of filling of left transverse sinus.
Media file 7: Case 2: Axial view of MR venogram demonstrating lack of flow in transverse sinus.

Media file 8: Case 2: Coronal view of MR venogram demonstrating lack of flow in the left transverse and sigmoid sinuses.

REFERENCES

Section 11 of 11
References
