CME

# Evidence-Based Practice

Answering clinical questions with the best sources

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## WHAT'S INSIDE



IN THE NEWS

# Minocycline shows promise for stroke neuroprotection

Stroke leads to significant morbidity and mortality in the United States. Each year about 500,000 people experience a new stroke and 200,000 have a recurrent stroke. Of these cerebral events, 88% are due to ischemic strokes, 9% are caused by intracerebral hemorrhage, and 3% are due to subarachnoid hemorrhage. About 10% of ischemic strokes and 35% of hemorrhagic strokes result in death within 30 days.[1] Risk factors for stroke include prior transient ischemic attacks, smoking, estrogen supplementation, atrial fibrillation, hypertension, diabetes, and lack of physical activity.

One recent estimate indicates that more than 1.1 million Americans suffer from functional limitations due to stroke. While two-thirds of stroke survivors eventually regain functional independence, 6 months after the event 50% of older adults have residual hemiparesis, 30% are unable to walk without some assistance, and 26% are institutionalized in a nursing home. The total estimated direct and indirect cost of stroke for 2006 was around $60 billion.[1]

Morbidity and mortality are reduced by rapid medical evaluation and intervention (**TABLE 1**).[2] At present, however, treatment options for acute ischemic stroke are limited. Though urgent administration of recombinant tissue plasminogen activator can remove the offending clot, many patients are not candidates to receive this agent (**TABLE 2**). Consequently, physicians and researchers active in stroke medicine seek alternative medications that act as direct neuroprotective agents.

## Minocycline possibly helpful

Researchers have been studying the use of minocycline as a neuroprotective agent in animal models, where it has proven effective.[3–5] Minocycline is a highly lipophilic antibiotic of the tetracycline class that can be given by either oral or intravenous routes. Postulated mechanisms for the protective effects seen in bench research include its anti-inflammatory action, reduction of microglial activation, enhanced nitric oxide production, and inhibition of apoptotic cell death.[6] In humans, a single oral minocycline dose of 200 mg is almost

**TABLE 1**

**Major recommendations for managing ischemic stroke[2]**

| |
|---|
| • Early activation of the emergency response system |
| • Use regional stroke centers, stroke units, and stroke protocols |
| • Brain imaging completed within 45 minutes of arrival |
| • If an rtPA candidate, lower BP to <185/110 mmHg |
| • rtPA for appropriate candidates (see Table 2) |
| • Intraarterial thrombolysis if <6 hours after occlusion of middle cerebral artery and not an rtPA candidate |
| • Swallowing evaluation and early mobilization |
| • Use some form of DVT prophylaxis |
| • Start aspirin within 24–48 hours |
| • Decompression of unknown value (except for surgical evacuation of space-occupying cerebellar infarcts) |
| • No putative neuroprotective interventions yet recommended |

BP=blood pressure; DVT=deep vein thrombosis; rtPA=recombinant tissue plasminogen activator.

**TABLE 2**

**Criteria for administration of recombinant tissue plasminogen activator (rtPA)[2]**

| |
|---|
| • Ischemic stroke with nontrivial deficit |
| • Neurologic signs not clearing spontaneously |
| • Onset of symptoms <3 hours before |
| • No myocardial infarction within 3 months |
| • No head trauma or prior stroke within 3 months |
| • No GI or GU hemorrhage within 3 weeks |
| • No major surgery in 2 weeks |
| • No arterial puncture at a noncompressible site within 1 week |
| • No history of intracranial hemorrhage |
| • Blood pressure <185/110 mmHg |
| • No active bleeding or acute fracture at presentation |
| • INR ≤1.7 |
| • Platelet count ≥100,000 mm$^3$ |
| • Blood glucose concentration ≥50 mg/dL (2.7 mmol/L) |
| • No seizure or postictal residua |
| • CT does not show multilobar infarction |
| • Patient and/or family adequately counseled about risks and harms |

CT=computed tomography; GI=gastrointestinal; GU=genitourinary; INR=international normalized ratio.

completely absorbed and produces a serum level of 6 µg/mL. Brain levels are approximately 50% of peak serum levels.[5]

## The study

Recently, in a prospective, open-label, evaluator-blinded clinical trial, patients were treated with either 200 mg oral minocycline or placebo once daily for 5 days after an acute ischemic stroke.[6] The primary outcome measure was the NIH Stroke Scale (NIHSS) score on day 90 after the event. NIHSS scores on days 7 and 30 were also evaluated as secondary outcomes. The NIHSS assesses 13 aspects of a patient's neurological status and runs from 0 (no impairment) to 34 (coma with flaccid paralysis).

Patients were required to be older than 18 years, have an initial NIHSS score of more than 5, and have had stroke onset between 6 and 24 hours of beginning treatment. Patients with hemorrhagic strokes, other CNS disease or disability, swallowing difficulties, or renal impairment, and patients requiring other antibiotics were excluded. The study was powered to have an 80% chance of detecting a difference of 2 to 4 NIHSS points between the 2 groups at day 90.

A total of 152 patients participated in the study (35% were female; mean age, 67 years). The average time from stroke onset to treatment with the study compound was 12 hours. No patients were lost to follow-up, although 14 died (5 in the minocycline group and 9 in the control group). Randomization failures resulted in the minocycline group having significantly more patients with a history of peptic ulcer disease (12% vs 1%), more patients taking sulfonylureas (16% vs 4%), and fewer patients taking angiotensin-converting enzyme inhibitors (34% vs 52%) than the placebo group ($P$<.02 for all comparisons). The groups were similar in demographics, risk factors, admission treatment, stroke type, and NIHSS scores at presentation.

## Results

At day 90, NIHSS scores were significantly lower in the minocycline- versus placebo-treated patients (1.6±1.9 vs 6.5±3.8; $P$<.0001). This effect was already apparent at day 7 and persisted throughout the follow-up. Adjusting for the different medication profiles slightly increased the magnitude of the effect. No

difference in effect was noted based on stroke size, although subgroups were small.

## Summary

This trial was a preliminary study with several weaknesses: it was not double-blinded; treatment was limited to the oral route; and it excluded patients with dysphagia. However, the result—a significant outcome difference 3 months after an ischemic stroke—indicates that an inexpensive, noninvasive treatment may offer hope to ischemic stroke suffers. Further studies of the use of minocycline acute stroke care are eagerly anticipated. EBP

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# HelpDesk

CONCISE ANSWERS TO PHYSICIANS' CLINICAL QUESTIONS

### The HelpDesk Search Strategy

HelpDesk Answers are intended to provide the same quality response to a clinical question as would be achieved by a search-savvy physician spending an hour or so on the Internet. Authors of HelpDesk Answers are required to search PrimeEvidence (http://www.primeanswers.org) and the TRIP database (www.tripdatabase.com). These portals provide access to more than a dozen sources of the highest quality evidence-based clinical information, including BMJ Clinical Evidence, the Guide to Clinical Preventive Services, AHRQ Evidence Reports, and others. Searches of the Cochrane Database, Medline, and other databases are also included, as needed.

## How accurate are blood glucose meters?

### Evidence-Based Answer

Approximately half of patients report blood glucose readings with an error rate of more than ±10% of the laboratory value. (SOR **B**, based on cross-sectional studies.) The American Diabetes Association (ADA) recommends healthcare providers evaluate a patient's blood glucose monitoring technique during initiation of self-monitoring, and then subsequently at regular intervals. (SOR **C**, based on consensus opinion.)

In 1996 the ADA recommended glucose meters achieve a total error of <10%, and in the future should achieve a total error of ~5%.[1] In the ADA's most current "Standards of medical care in diabetes," there is no mention of meter accuracy goals.[2] The ADA did, however, recommend physicians evaluate technique at initiation of self-monitoring and then at regular intervals thereafter based on user and meter differences.

A cross-sectional study conducted in 2004 examined meter accuracy for 102 patients with type 1 and type 2 diabetes by comparing results obtained by a patient with his or her own glucometer versus a serum laboratory sample.[3] Readings were within ±10% of the laboratory value for 45% of the 102 patients (46/102) and readings within ±15% of the laboratory value for 55% of the patients (56/102). Overall, patients' meters overread the lab values by 13.67% ($P$=.001).

A similar study performed at 2 family practice residency sites in 2002 compared blood glucose values of 108 patients with type 1 and 2 diabetes who had been using a glucose meter an average of 2.8 years.[4] Glucose levels were self-determined with the patients' meters and with a meter used at the study site. They reported 52.8% of the