

endarterectomy group) and ipsilateral stroke (6% in the stenting group vs. 5% in the endarterectomy group).

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Artesunate for Malaria

TO THE EDITOR: Rosenthal (April 24 issue)¹ presents a hypothetical case of malaria and states that there is “major concern” about the timeliness of artesunate availability because it is available rapidly only for hospitals that are near the 20 Centers for Disease Control and Prevention (CDC) quarantine stations. Artesunate is stocked at 8 of the 20 stations, which are located at major U.S. airports. To date, the timeliness of the provision of artesunate has been quite reasonable. Among the actual cases of the disease, on average it has taken only 7 hours (range, 3.5 to 15.5) from the time of the request for artesunate until the patient receives the first dose; 73% of the patients treated have been in hospitals that are not near CDC quarantine stations (average distance, 480 miles [772 km]; range, 66 to 1448 [106 to 2330]). To date, all patients treated according to this protocol have recovered. The CDC will continue to provide artesunate until it becomes a Food and Drug Administration (FDA)–approved, commercially available product and hospitals can maintain their own supply. Meanwhile, the current system can provide artesunate rapidly, and health care providers should be encouraged to access this medicine for the treatment of severe malaria.

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TO THE EDITOR: I would like to make some additional comments regarding the toxic effects of artemisinin antimalarial drugs, since these effects

are briefly mentioned in Rosenthal’s article. Neurotoxic effects have been observed in animals treated with intramuscular artemisinin in oil-based formulations. However, clinical reports on such toxic effects are rare and inconclusive, despite the large pool of treated patients. The same derivatives given intramuscularly but with the use of a water-based formulation do not have toxic effects in animals.¹

A colleague and I have argued that changes in the pharmacokinetics of artemisinin due to a prolonged absorption after repeated oil-based intramuscular injections cause the observed toxic effects in animals.² Oral and intravenous injections are the most common routes of administration in humans, and with the short half-life of these drugs, the risk of toxic effects seems minimal. Even the intramuscular injections may not be of concern because of the limited number of injections.

When investigating the efficacy and toxicity of drugs, it is imperative to consider their pharmacokinetic properties.

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TO THE EDITOR: Rosenthal provides an excellent review of artesunate for the treatment of severe falciparum malaria. However, many physicians are unaware that the onset of symptoms may be delayed among Americans with malaria.

From 1992 to 1998, a total of 5185 cases of malaria were diagnosed in the United States. In 35% of the patients, the symptoms started more

than 2 months after a return from travel.¹ Malaria typically occurs in travelers because of a lack of pretravel health information and poor compliance with a recommended antimalarial regimen. The diagnosis of late-onset illness in travelers who have used such a regimen is more challenging for physicians and may be more difficult for patients to associate with previous travel. Physicians should consider malaria in patients whose symptoms started more than 2 months after a return from international travel.

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TO THE EDITOR: Rosenthal makes no mention of the enormous life-threatening problem of fake artemisinin compounds that are being produced, marketed, and used in Third World countries. Because artesunate is an effective and important antimalarial agent, a flourishing counterfeit trade has arisen. The rapid action and relatively high cost of artesunate make it particularly attractive to counterfeiters. In a survey conducted in five countries in Southeast Asia, 38% of artesunate tablets were fake.¹ Fake tablets, capsules, dry suspensions, and injections of artemisinin compounds, including artesunate, have been identified in Kenya and the Democratic Republic of Congo. Almost 40% of these drugs were produced in India.

In India, counterfeit drugs are estimated to account for 13 to 30% of the pharmaceutical market; this has led to a recent discussion of the death penalty for counterfeiters.² Fake artesunate contributes to the morbidity and mortality associated with malaria and gives rise to misperceptions of artesunate “resistance.”³ International organizations, including the World Health Organization and member countries, have been unable to counter this lethal trade.^{2,4}

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THE AUTHOR REPLIES: Arguin and colleagues indicate that the new system for rapid distribution of intravenous artesunate in the United States has led to acquisition of the drug within 3.5 to 15.5 hours after requests for it, with recovery from malaria in all cases. However, severe malaria should be treated as rapidly as possible, ideally less than 3 hours after diagnosis. Thus, a routine commercial supply of intravenous artesunate will be an important advance.

The neurotoxicity of artemisinins, which has been shown in laboratory animals that receive dosages much higher than those used to treat malaria, has been extensively studied.¹ I agree with Gordi's impression that neurotoxicity is unlikely to be of relevance with the clinical use of artemisinins, and in particular artesunate. Indeed, the test of time has shown artemisinins to be remarkably safe. However, formal surveillance for artemisinin toxicity has to date been somewhat limited, and it is important to maintain vigilance regarding the possibility of rare but potentially life-threatening toxic effects from this very important class of antimalarial agents.

Itskowitz notes that presentation with malaria may be delayed until well after the time of exposure. This is a valuable point, and malaria should be considered to be a cause of fever, even many months after a return from travel. However, patients with malaria caused by *Plasmodium falciparum*, which is responsible for nearly all cases of severe malaria, are much less likely to present late than are patients with malaria caused by other species. CDC statistics show that among the 668 patients with a diagnosis of malaria in the United States in 2005 for whom the timing of presentation was known, 94% of those with falciparum malaria became ill before or within 1 month after

a return from travel in a country where malaria is endemic.²

The concern raised by Kashyap and colleagues regarding counterfeit artemisinins is well founded. The use of substandard or counterfeit drugs may seriously jeopardize the successful use of artemisinin-based combination therapies, the new standard for the treatment of uncomplicated falciparum malaria in most of the world.³ My review focused on intravenous artesunate for severe malaria. There is also a risk of counterfeit intravenous formulations in some developing countries, but it is unlikely that

counterfeit drugs will endanger the supply of intravenous artesunate in the United States.

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Case 12-2008: Apnea and Seizures in a Newborn Infant

TO THE EDITOR: Redline et al. (April 17 issue)¹ discuss an interesting case of a newborn with seizures and apnea secondary to perinatal ischemic stroke. Although an accurate diagnosis was made without the use of lumbar puncture and cerebrospinal fluid analysis, we think these tests should have been performed.

As the authors state, intracranial hemorrhage, especially subarachnoid hemorrhage, is a common cause of neonatal seizures. Although a computed tomographic (CT) scan of the head showed no evidence of subarachnoid hemorrhage, small subarachnoid hemorrhages are often diagnosed only with cerebrospinal fluid analysis.

In addition, as the authors mention, meningitis is a possibility, especially given maternal chorioamnionitis. Although blood cultures were negative, blood cultures may be negative in neonates with documented bacterial meningitis.^{2,3} Herpes simplex virus (HSV) meningitis is another possibility. Despite no maternal history of HSV infection, the temporal-lobe hypodensity on the CT scan mandates its consideration.

Retrospectively, although cerebrospinal fluid analysis was not required to make the correct diagnosis, we believe the authors should have emphasized that in the workup of a neonate with seizures and apnea, lumbar puncture should be strongly considered.

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TO THE EDITOR: Redline and colleagues do not mention possible maternal cocaine use and consequent fetal exposure to the drug as a possible risk factor for perinatal stroke. The maternal history neither included nor excluded this important risk factor. A neuroradiologic study¹ showed that 17% of newborns who had been exposed in utero to cocaine had cerebral infarction, as compared with 2% of newborns in the control group. In particular, the authors postulated that the significantly higher frequency of stroke among the newborns who had been exposed in utero was related to vasospasm caused by cocaine when used in the third trimester of pregnancy. Even though perinatal stroke is considered to be a multiple-risk-factor disease,² cocaine abuse during pregnancy is the only risk factor that is 100% preventable. Physicians should therefore emphasize the potentially adverse effects of drug abuse in any pregnancy.

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