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Commentary on Miura

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Dr. Miura's study evaluated the use of zonisamide in children with cryptogenic localization-related epilepsy, as monotherapy in a single daily dose. All patients were naive to anticonvulsant therapy. The study examined both clinical effects and pharmacokinetic effects of zonisamide. Patients ranged in age from infancy (3 months) to 15 years of age, with a mean age of 8 years. All were of normal intelligence and did not have concomitant psychiatric illnesses. Thus, the group was homogeneous.

Earlier studies had shown that the plasma concentration of zonisamide peaks at 4 h, and that its half-life in healthy volunteers is about 60 h. These findings were the groundwork for examining whether single-dose monotherapy of zonisamide is effective for epilepsy treatment. Patients received zonisamide in the morning at an initial dose of 2 mg/kg per day, which was increased incrementally to an 8 mg/kg per day maintenance dose. Blood samples were taken to determine trough and peak plasma levels of the drug. Pharmacokinetic studies showed plasma level-to-dose ratios increased with age, but peak-to-trough plasma level ratios did not.

Dr. Miura and colleagues found that 57 of the 72 patients (79%) achieved complete seizure control over a treatment period of 6–43 months (mean 27 months). Efficacy data showed that the therapeutic range is somewhere from 15 to 40 μg/mL, with 15 μg/mL being subtherapeutic for seizure control in many, and 40 μg/mL being toxic in others. Low plasma levels of zonisamide explained why some patients' seizures were not controlled, but for others, increasing zonisamide levels did not improve seizure control.

Adverse effects of note were drowsiness and ataxia, which are seen with many other antiepileptic drugs (AEDs); and anorexia, which is also seen with two of the newer AEDs—felbamate and topiramate. One patient experienced a rash with agranulocytosis early in treatment; again, this has been seen with other AEDs. Overall, the number of patients who experienced adverse events with monotherapy was small; nevertheless, it is important to recognize the potential for such events.

For patients whose seizures were uncontrolled with zonisamide ($n = 12$), carbamazepine was added to the treatment regimen. Pharmacokinetic data showed that carbamazepine reduced zonisamide plasma levels, consistent with the cytochrome-inducing capacity of carbamazepine. However, zonisamide had no impact on carbamazepine levels.

Of the 12 patients whose seizures were not controlled by zonisamide monotherapy despite an increase in dose, six became seizure-free with the addition of carbamazepine. Seizures were controlled in three additional patients by switching to other anticonvulsants—valproate or clonazepam. For the remaining three patients, seizures remained refractory.

In summary, Dr. Miura's study shows that zonisamide is effective as single-dose monotherapy in young patients with cryptogenic localization-related epilepsy. However, proper dosage must be determined on a case-by-case basis, as is true

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with other AEDs. Zonisamide dosage should be determined with attention to plasma levels that may be too low and potentially subtherapeutic, or too high and therefore toxic. In addition, although adjunctive treatment with carbamazepine can improve seizure control in patients for whom zonisamide monotherapy is ineffective, physicians should be aware that cytochrome inducers such as carbamazepine will affect zonisamide levels and potentially seizure control.