Doctor on Call

Julia, a 24-year-old aspiring chef who lives in Santa Fe writes:

I've had migraine since my early teenage years, and while my headaches can be triggered by skipping meals or too little sleep, they more often occur for no rhyme or reason. I usually can control them with an oral medication. The exception is when I wake up in the morning with a headache that's already severe. My usual oral medication does absolutely nothing to help, and I simply lie down in a dark quiet room and ride it out. Not a good thing for my job at the restaurant where I work as a pastry chef.

Eventually my doctor prescribed injectable sumatriptan, and its effect the first few times I used it was nothing short of miraculous. My headache, nausea and light sensitivity were completely gone within 15 minutes, and each time I avoided losing a day of my life (and potentially my job).

More recently I have had a few episodes of wake-up-with-it migraine where the injectable sumatriptan worked just fine… but then the headache returned with a vengeance just two or three hours later. Am I having rebound headachea? I use either my oral triptan or the injectable sumatriptan about five or six days every month. Is that too much?

Worried in Santa Fe

The Doctor's Reply:

Julia,

What you are experiencing is quite common, and it does not result from overuse of the triptans, which is what I presume you, like many, are equating with "rebound" headache.

The toughest migraine headaches are those that have been developing biologically and clinically for a while and have escalated to the point where the pain intensity has reached the level of "severe". This is often the case when the acute migraine process begins while one is still asleep, and once awake the process is too far along its biologic path for an oral medication to catch up.

The beauty of injectable sumatriptan is that after administration it reaches its peak blood level far more quickly than any orally administered medication, and the concentration of sumatriptan in the blood also is significantly higher than what is achieved with an oral equivalent. Presumably this results in faster delivery of more drug to its intended targets within the migraine circuitry. When migraine headache has progressed to the level of severe intensity, there is "need for speed", and injectable sumatriptan is a Ferrari compared to the Prius of oral medication.

The downside of injectable sumatriptan is it's short biologic half-life in the body. Within a matter of a few hours the injected sumatriptan is virtually gone, and unless the roaring fire of the acute migraine was entirely extinguished, it is quite likely to flare up once again. The drug didn't fail; it just didn't hang around long enough complete the job. Patients often characterize this early recurrent headache following initially successful treatment with injectable sumatriptan as "rebound" and assume that in some way or another it was the medication that caused this frustrating outcome.

So what can you do to eliminate the early recurrent headache associated with use of injectable sumatriptan? While it's true that administering the medication without delay, as soon as the headache is moderate to severe intensity, and thereby achieving complete headache relief rather than a reduction in pain lessens the likelihood of early recurrent headache, that strategy is not much help if you are asleep as the migraine is developing.

One obvious option is to anticipate the possibility of early recurrent headache and be ready to administer appropriate oral medication as soon as the recurrent headache begins to develop. Although to do so as "off-label" and lacking a strong evidence base, some physicians advise patients who consistently experience early recurrent headache following use of injectable sumatriptan to administer an oral triptan simultaneous with the

injection. The logic is that the oral triptan will be coming on board at about the same time the injectable sumatriptan is exiting the body.

Another option is to treat the initial headache with a medication that has a longer biologic half-life in the body and is associated with a lower likelihood of early headache recurrence. We already have established that oral medications, long half-life or no, typically are too slow in onset to be affective in the setting, but there are alternatives. The half-life of zolmitriptan (*Zomig*) administered as an intra-nasal spray is somewhat longer than that of injectable sumatriptan; in terms of its rapidity of therapeutic action, zolmitriptan nasal spray is slower than the injectable drug but faster than the oral triptans.

Another interesting option is dihydroergotamine (DHE), and old drug chemically related to the triptans which often is administered intravenously for acute migraine headache that resists self-administered treatment. There is no autoinjector for DHE as there is for sumatriptan, but if your healthcare provider is willing and able to teach you, it can be self-administered subcutaneously/under the skin using a syringe and very small needle. In a head-to-head trial comparing subcutaneously administered DHE with injectable sumatriptan, the DHE was a bit slower to act in relieving headache but, as would be expected from its much longer half-life, was associated with a far lower frequency of early recurrent headache. An intranasal formulation of DHE (*Trudhesa*) is featured in this issue as a "migraine treatment of the month", and because the spray containing the medication reaches a portion of the nose richly supplied by blood vessels, the DHE gets to where you want it to go quite rapidly. For some migraineurs who consistently experience early recurrent headache with injectable sumatriptan or who prefer not to self-inject for headache "rescue", *Trudhesa* may prove to be an especially attractive alternative.

Hope this helps, Julia, and good luck with the job. We always need more good chefs.

FOR THE ACUTE TREATMENT OF MIGRAINE

Trudhesa®
(dihydroergotamine mesylate) nasal spray

0.725 mg per spray

THINK YOU'VE TRIED EVERYTHING FOR MIGRAINE?

YOU HAVEN'T TRIED ANYTHING LIKE THIS

Trudhesa® uses a high-tech little device called POD® (or Precision Olfactory Delivery) to gently deliver trusted medication

When used to treat 4515 migraine attacks in a 24-week safety study, exploratory results showed that for some people, Trudhesa was*:

Speedy
Pain relief can start in as few as 15 minutes

Steady
Pain freedom can last 2 days with just 1 dose

At the ready
Designed to deliver pain freedom even when taken late into an attack

*Exploratory efficacy outcomes are based on patient reports and post hoc analyses from a phase 3, open-label safety study of Trudhesa.

Important Safety Information

Indication

Trudhesa is used to treat an active migraine headache with or without aura in adults. Do not use Trudhesa to prevent migraine when you have no symptoms. It is not known if Trudhesa is safe and effective in children.

Serious or potentially life-threatening reductions in blood flow to the brain or extremities due to interactions between dihydroergotamine (the active ingredient in Trudhesa) and strong CYP3A4 inhibitors (such as protease inhibitors and macrolide antibiotics) have been reported rarely. As a result, these medications should not be taken together.

Please see full Important Safety Information and Brief Summary of the full Patient Information on the following pages.

With Trudhesa Direct™, you can get your prescription for just $10† if you're commercially insured, delivered straight to your door at no extra cost

Pay as little as **$10** for Trudhesa†

If you're facing financial hardship or have limited or no insurance coverage, Impel Pharmaceuticals Patient Assistance Program is here to help. You can enroll in the program by calling customer care at **1-833-TRUDHESA (833-878-3437)**, option 2.

Still have questions about Trudhesa? Scan the QR code or visit trudhesa.com/FAQs to learn more

Important Safety Information (continued)

Do not use Trudhesa if you:

- Have any disease affecting your heart, arteries, or blood circulation
- Are taking certain anti-HIV medications known as protease inhibitors (such as ritonavir or nelfinavir)
- Are taking a macrolide antibiotic such as clarithromycin or erythromycin
- Are taking certain antifungals such as ketoconazole or itraconazole
- Have taken certain medications such as triptans or ergot-type medications for the treatment or prevention of migraine within the last 24 hours
- Have taken any medications that constrict your blood vessels or raise your blood pressure
- Have severe liver or kidney disease
- Are allergic to ergotamine or dihydroergotamine

Before taking Trudhesa, tell your doctor if:

- You have high blood pressure, chest pain, shortness of breath, heart disease; or risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease or you are postmenopausal, or male over 40); or problems with blood circulation in your arms, legs, fingers, or toes.
- You have or had any disease of the liver or kidney.
- You are taking any prescription or over-the-counter medications, including vitamins or herbal supplements.
- You are pregnant, planning to become pregnant or are nursing, or have ever stopped medication due to an allergy or bad reaction.
- This headache is different from your usual migraine attacks.

The use of Trudhesa should not exceed dosing guidelines and should not be used on a daily basis.

Serious cardiac (heart) events, including some that have been fatal, have occurred following the use of dihydroergotamine mesylate, particularly with dihydroergotamine for injection, but are extremely rare.

You may experience some nasal congestion or irritation, altered sense of taste, sore throat, nausea, vomiting, dizziness, and fatigue after using Trudhesa.

Contact your doctor immediately if you experience:

- Numbness or tingling in your fingers and toes
- Severe tightness, pain, pressure, heaviness, or discomfort in your chest
- Muscle pain or cramps in your arms or legs
- Cold feeling or color changes in 1 or both legs or feet
- Sudden weakness
- Slurred speech
- Swelling or itching

The risk information provided here is not comprehensive. To learn more, talk about Trudhesa with your healthcare provider or pharmacist. The FDA-approved product labeling can be found at www.trudhesa.com or 1-800-555-DRUG. You can also call 1-833-TRUDHESA (1-833-878-3437) for additional information.

Please see Brief Summary of the full Patient Information on the following page.

†**Terms and Conditions:** The pharmacy will enroll you into the Trudhesa Direct Patient Savings Program. This offer cannot be redeemed for cash. Each time the offer is used, you are certifying that you meet the eligibility criteria and will comply with the terms and conditions described in the Restrictions section below. If you have any questions about this offer, please call **1-833-TRUDHESA (833-878-3437)**.

Restrictions: This offer is valid in the United States only. Offer is available if a patient has a prescription, is commercially insured and is 18 years or older. Offer is not valid for patients who use any state or federal government-funded healthcare program to cover a portion of medication costs, such as Medicare (including Medicare Part D), Medicaid, Medigap, TRICARE, Department of Defense (DOD), Veterans Administration (VA), patients who are cash-paying or where prohibited by law. By using this offer, the patient certifies that he or she will comply with any terms of his or her insurance plan. It is illegal to (or offer to) sell, purchase, or trade this offer. Void where prohibited by law. This program does not constitute health insurance. Program managed by ConnectiveRx on behalf of Impel Pharmaceuticals. The parties reserve the right to rescind, revoke or amend this offer without notice at any time.

Impel PHARMACEUTICALS

TRUDHESA® (dihydroergotamine mesylate) nasal spray, 0.725 mg per spray
BRIEF SUMMARY OF PRESCRIBING INFORMATION

(For complete details, please see full Prescribing Information and Medication Guide.)

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT TRUDHESA?

Serious or potentially life-threatening reductions in blood flow to the brain or extremities due to interactions between dihydroergotamine (the active ingredient in Trudhesa) and strong CYP3A4 inhibitors (such as protease inhibitors and macrolide antibiotics) have been reported rarely. As a result, these medications should not be taken together. Stop taking Trudhesa and get emergency medical help right away if you have any of the following symptoms: cramping and pain in your legs or hips, feeling of heaviness or tightness in your leg muscles, burning or aching pain in your feet or toes while resting, numbness, tingling, or weakness in your legs, cold feeling or color changes in 1 or both legs or feet, slurred speech, or sudden weakness.

WHAT IS TRUDHESA?

Trudhesa Nasal Spray is used to treat an active migraine headache with or without aura in adults. Do not use Trudhesa to prevent migraine when you have no symptoms. Trudhesa is not used to treat other types of headaches such as hemiplegic (that make you unable to move on one side of your body) or basilar (rare form of migraine with aura) migraines. It is not known if Trudhesa is safe and effective in children.

DO NOT TAKE TRUDHESA IF YOU:

- Are taking medicines known as strong CYP3A4 inhibitors (such as ritonavir or nelfinavir).
- Have heart problems or a history of heart problems.
- Have uncontrolled high blood pressure.
- Have narrowing of blood vessels in your legs, arms, stomach, or kidneys (peripheral vascular disease).
- Have sepsis.
- Have had vascular surgery.
- Have severe liver problems.
- Have severe kidney problems.
- Are allergic to dihydroergotamine mesylate, ergot alkaloids, or any ingredients in Trudhesa.
- Have taken any of the following medicines in the last 24 hours: sumatriptan, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, or ergotamine or ergotamine-type medicines.
- Have taken any medicines that constrict your blood vessels or raise your blood pressure.

Ask your healthcare provider if you are not sure if you are taking any of these medicines.

DO NOT USE TRUDHESA IF YOU:

- Have any disease affecting your heart, arteries, or blood circulation.
- Are taking certain anti-HIV medications known as protease inhibitors (such as ritonavir or nelfinavir).
- Are taking a macrolide antibiotic such as clarithromycin or erythromycin.
- Are taking certain antifungals such as ketoconazole or itraconazole.
- Have taken certain medications such as triptans or ergot-type medications for the treatment or prevention of migraine within the last 24 hours.
- Have taken any medications that constrict your blood vessels or raise your blood pressure.
- Have severe liver or kidney disease.
- Are allergic to ergotamine or dihydroergotamine.

BEFORE TAKING TRUDHESA, TELL YOUR DOCTOR IF:

- You have high blood pressure, chest pain, shortness of breath, heart disease; or risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease or you are postmenopausal, or male over 40); or problems with blood circulation in your arms, legs, fingers, or toes.
- You have or had any disease of the liver or kidney.
- You are taking any prescription or over-the-counter medications, including vitamins or herbal supplements.
- You are pregnant, planning to become pregnant or are nursing, or have ever stopped medication due to an allergy or bad reaction.
- This headache is different from your usual migraine attacks.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Your healthcare provider will decide if you can take Trudhesa with your other medicines.

Especially tell your healthcare provider if you take: sumatriptan, ergot-type medicine, saquinavir, nefazodone, fluconazole, grapefruit juice, zileuton, nicotine, propranolol or other medicines that can lower your heart rate, any medicines that can increase your blood pressure, or selective serotonin reuptake inhibitors.

These are not all of the medicines that could affect how Trudhesa works. Your healthcare provider can tell you if it is safe to take Trudhesa with other medicines.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF TRUDHESA?

Trudhesa can cause serious side effects, including:

- **Heart attack and other heart problems.** Heart problems may lead to death. Stop taking Trudhesa and get emergency medical help right away if you have any of the following symptoms of a heart attack: discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back; severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw; pain or discomfort in your arms, back, neck, jaw, or stomach; shortness of breath with or without chest discomfort; breaking out in a cold sweat; nausea or vomiting; or feeling lightheaded.
  - Trudhesa is not for people with risk factors for heart disease unless a heart exam is done and shows no problem. You have a higher risk for heart disease if you have high blood pressure, have high cholesterol levels, smoke, are overweight, have diabetes, or have a family history of heart disease.
- **Stroke.** Stop taking Trudhesa and get emergency medical help right away if you have any of the following symptoms of a stroke: face drooping, unusual weakness or numbness, or slurred speech.
- **Changes in color or sensation in your fingers and toes (Raynaud's syndrome).**
- **Stomach and intestinal problems** (gastrointestinal and colonic ischemic events). Symptoms of gastrointestinal and colonic ischemic events include sudden or severe stomach pain, constipation or diarrhea, stomach pain after meals, bloody diarrhea, weight loss, fever, or nausea or vomiting.
- **Increase blood pressure.**
- **Medicine overuse headache.** Some people who use too much Trudhesa may make their headaches worse (medicine overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with Trudhesa.
- **Preterm labor.**
- **Tissue changes (fibrotic complications).** Inflammation and fiber-like tissue that is not normal (fibrosis) can occur around the lungs and stomach.
- **Burning feelings in your nose, mouth, and throat and abnormal taste.**

The most common side effects of Trudhesa include runny nose, application site reactions, sleepiness, nausea, dizziness, sore throat, abnormal taste, vomiting, and diarrhea.

These are not all the possible side effects Trudhesa. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

The risk information provided here is not comprehensive. To learn more, talk about Trudhesa with your healthcare provider or pharmacist. The FDA-approved product labeling can be found at www.trudhesa.com or 1-800-555-DRUG. You can also call 1-833-TRUDHESA (1-833-878-3437) for additional information.

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