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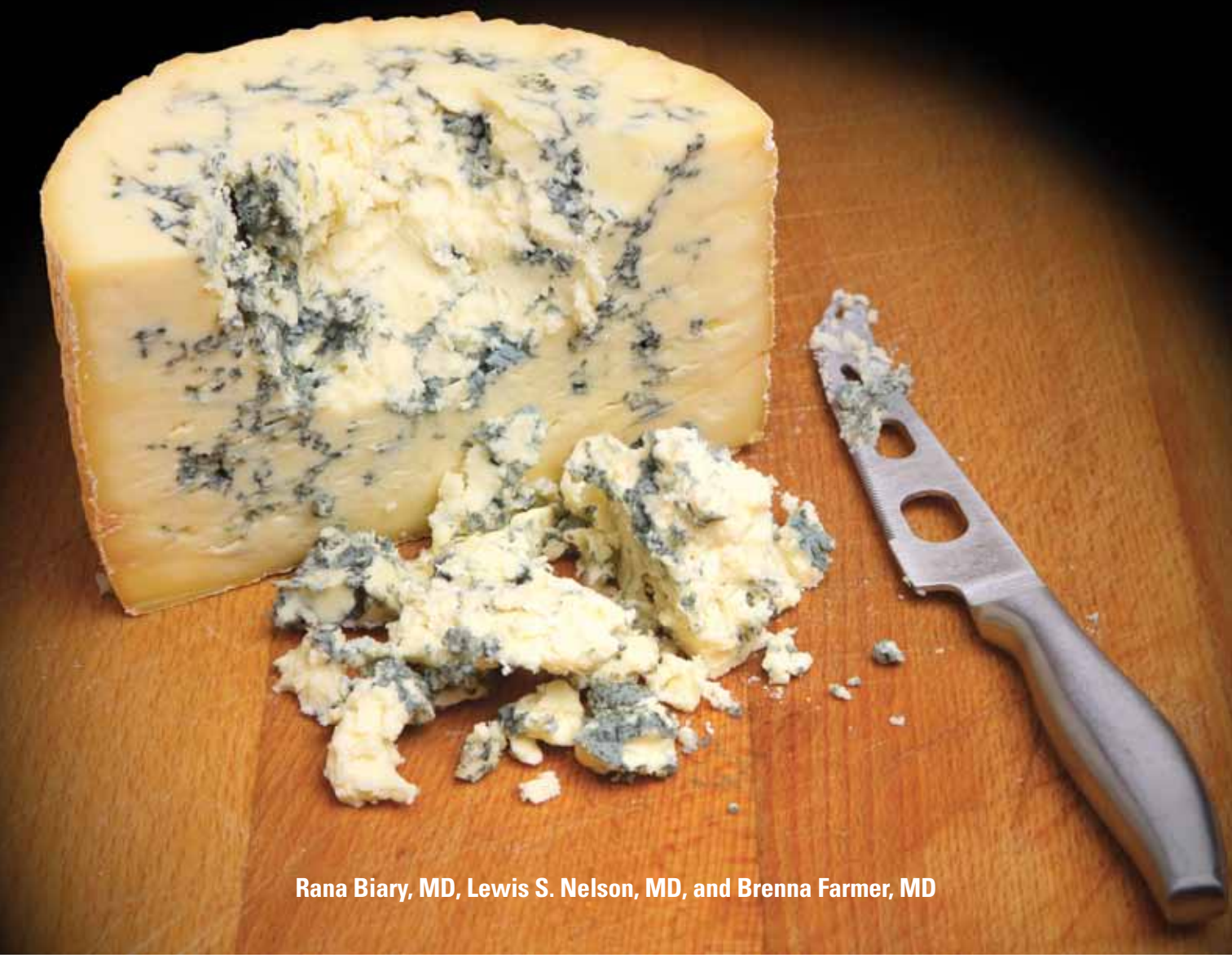
A Moment on Your Lips…



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A 61-year-old man develops severe headache, palpitations, abdominal pain, and chest pain immediately following a midday snack.

A 61-year-old man with a history of coronary artery disease, hypertension, hyperlipidemia, and depression presents to the ED complaining of severe headache, palpitations, abdominal pain, and chest pain, which he states developed immediately following a midday snack. He denies use of alcohol or illicit drugs and has

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not had any recent changes to his medication regimen. His vital signs are: blood pressure (BP), 228/114 mm Hg; heart rate, 56 beats/min; respiratory rate, 16 breaths/min; temperature, afebrile. Oxygen saturation is 97% on room air. The patient's physical examination is within normal limits. A bedside abdominal sonogram shows a normal abdominal aorta of 2.5 cm in diameter.

The patient receives metoclopramide and morphine for his headache. A computed tomography of the head is unremarkable. The patient's initial serum troponin is negative, with an electrocardiogram (ECG) showing sinus bradycardia in the range of 40 beats/min, with no acute ST-T wave changes.

What are some of the pharmacotherapeutic causes of hypertension?

Many therapeutic drugs, particularly in overdose, can elevate BP. For example, amphetamine causes central nervous system (CNS) sympathetic overactivity by increasing the release of catecholamines and decreasing their reuptake from the synapses.[1] This leads to both peripheral vasoconstriction (α_1-adrenergic receptor-induced) and increased inotropy (β_1- and β_2-adrenergic receptor-induced), which results in elevated BP, tachycardia, diaphoresis, and dilated pupils, all consistent with the sympathomimetic toxidrome.[2]

In cases of overdose, certain medications will initially cause hypertension, followed by hypotension. For instance, clonidine, guanabenz, and guanfacine are all structurally similar and act centrally as α_2-adrenergic receptor agonists.[2] At initial presentation of an overdose, however, the peripheral α_2-adrenergic effects may predominate, causing pronounced hypertension.[3] Excessive doses of centrally acting α_2-adrenergic receptor agonists typically lead to depressed mental status and respiratory rate.

In contrast to clonidine, yohimbine, an alternative sexual enhancement agent, is a centrally acting α_2-adrenergic receptor antagonist. In overdose, hypotension may occur initially due to vasodilation resulting from the blockade of peripheral α_2-adrenergic receptors. Central effects eventually prevail and cause enhanced sympathetic output and sympathomimetic effects.[2]

Case continuation

The patient's spouse arrived at bedside an hour after presentation and provided additional history—notably, that the patient has been taking tranylcypromine (a monoamine oxidase inhibitor [MAOI]) 70 mg daily for longer than 20 years for depression. She further stated that he had consumed a snack consisting of aged cheese approximately 20 minutes before onset of symptoms.

Why are monoamine oxidase inhibitors of concern?

MAOIs, such as norepinephrine, serotonin, and dopamine, are neurotransmitters that are deaminated by MAO in the presynaptic terminal following reuptake. MAO exists in two forms, each with distinct anatomic and physiologic characteristics. MAO-A, though most prominent in the intestines and liver, is responsible for metabolizing serotonin and norepinephrine in the CNS. When MAO-A is inhibited by an MAOI, the elevated synaptic concentration of serotonin produces an antidepressant effect. The second type, MAO-B, is preferentially located in the CNS and metabolizes dopamine. MAO-B inhibitors are used to treat Parkinson disease.[2]

Tranylcypromine and phenelzine, the antidepressant MAOIs available in the United States, irreversibly inhibit both MAO-A and MAO-B.[4] Tyramine, like amphetamines, induces the release of norepinephrine at the synaptic terminal.[4] Although present in many foods, tyramine is metabolized by MAO-A in the intestinal wall and liver and is not systemically bioavailable.[2] In patients

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taking a nonselective MAOI (which inhibits MAO-A), ingestion of greater than 6 mg of tyramine can cause a hyperadrenergic crisis. Foods with a high content of tyramine include aged cheese, soy sauce, sauerkraut, certain wines and beers, and chicken liver.[5] Approximately 20% of patients on tranylcypromine will develop a hyperadrenergic crisis; in one case series, 6 of 27 crises were precipitated by consumption of cheese.[6] Of note, tranylcypromine is an amphetamine derivative and can lead to a hyperadrenergic crisis in overdose—independent of tyramine.[7]

Other causes of hyperadrenergic crisis in patients on MAOIs include amphetamine-like decongestants in cough and cold preparations (eg, pseudoephedrine). While the hyperadrenergic crisis is related to serotonin toxicity, it is a clinically distinct entity. Serotonin toxicity occurs in patients taking MAOIs in which triggers of presynaptic serotonin release, such as meperidine or dextromethorphan, produce muscle rigidity, hyperthermia, delirium, and tremor.

How should drug-induced hypertension be managed?

The decision to urgently lower a patient's BP is based on the presence of end-organ damage and not solely on numerical BP. A severe headache, for example, may not simply be due to hypertension but rather represents a hypertensive emergency resulting from cerebral edema or hemorrhage. If treatment for drug-induced sympathomimetic toxidrome is required, the sole use of a β-adrenergic receptor antagonist (β-blocker) to normalize vital signs is contraindicated. Because β-blockers block both β_1- and β_2-adrenergic receptors, the peripheral α-adrenergic receptors are unopposed, allowing enhanced peripheral and coronary artery vasoconstriction.[2,8,9]

Phentolamine, a short-acting α-adrenergic antagonist, lowers BP through vasodilation and is the preferred treatment agent.[2] Often, patients taking an MAOI are given a prescription for an immediate-release dihydropyridine calcium channel blocker (CCB), which may be utilized in the pre-hospital setting. CCBs, such as nifedipine, can also be administered in the ED.[10] Because the elevated BP and resulting headache are due to excessive CNS stimulation, benzodiazepines also have a therapeutic role.

Case conclusion

The patient was treated with diazepam, which lowered the BP and relieved his other symptoms; phentolamine was *not* required. He was then admitted to the hospital for observation and had serial troponin measurements that peaked at 0.46 ng/mL, without associated ECG changes. The inpatient team discussed changing the patient's antidepressant regimen, but he declined to do so, stating that tranylcypromine was the only medication that could successfully treat his depression. Upon discharge, patient was counseled to avoid consuming aged cheese, wine, and other tyramine-containing foods and decongestants.

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