Correspondance

Thermometer rising

John Sievenpiper and colleagues recently reported significantly higher blood glucose levels at 30, 45 and 60 minutes after a 900-mL meal than after a 600-mL or 300-mL meal of 75 g of glucose. Any increase in volume or decrease in osmolarity leading to an increase in the rate of gastric emptying during the first hour of the test with no effect on the result at 2 hours is intriguing.

There is also evidence that blood glucose levels might be affected by the ambient temperature. In Brazil, a 75-g load of glucose given to 1030 pregnant women resulted in a glucose concentration that was 0.2 mmol/L higher at 25–31°C than at 20–24°C. The corresponding value at 5–14°C was 1.03 mmol/L lower than at 25–30°C. This variable might affect test results in Canada given that ambient room temperature fluctuates. For the findings of Sievenpiper and colleagues to be beneficial globally, comprehensive investigations should be carried out at high and low ambient temperatures.

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References
1. Sievenpiper JL, Jenkins DJA, Josse RG, Vuksan V. Dilution of the 75-g oral glucose tolerance test increases postprandial glycemia: implications for diagnostic criteria. CMAJ 2000;162(7):991-6.

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Reactions to alteplase in patients with acute thrombotic stroke

Michael Hill and colleagues have made an important contribution by documenting the occurrence of serious adverse reactions to alteplase in pa-
patients treated for acute thrombotic stroke. I am concerned, however, by some of their comments.

Anaphylactic reactions and anaphylactoid reactions are distinct, and these terms should not be used interchangeably. Both are acute generalized reactions mediated by mast cell mediators such as histamine. With anaphylactic reactions, mast cell mediator release is triggered by IgE antibody to the causal agent (e.g., penicillin). With anaphylactoid reactions, mast cell mediator release is not mediated by IgE. This distinction has important diagnostic and management implications.

The authors suggest that their first patient “may have had an undiagnosed hereditary or acquired C1 esterase inhibitor deficiency.” Angioedema due to this deficiency is not characteristically associated with urticaria, which this patient exhibited. C2 and C4 are the natural substrates for C1 esterase activity and are typically depleted during acute angioedema provoked by C1 esterase inhibitor deficiency. Levels of C4 were reported to be normal in this patient, arguing strongly against C1 esterase inhibitor deficiency.

The authors comment that their “treatment with antihistamines and corticosteroids has been empirical and is based on the treatment of angioedema associated with hereditary or acquired deficiency in C1 esterase inhibitor.” Angioedema associated with this deficiency is notoriously resistant to treatment with antihistamines, corticosteroids and epinephrine. This refractoriness to conventional therapy is an important clue to the possibility of a deficiency in C1 esterase inhibitor. The only effective treatment of angioedema in this situation is perfusion with purified C1 esterase inhibitor, available from Canadian Blood Services. The most effective preventive measure is regular use of an attenuated androgen such as danazol.

The authors recommend caution treating patients receiving angiotensin-converting-enzyme inhibitors with alteplase because of the risk of angioedema. Angiotensin-converting-enzyme inhibitors are a well-documented cause of angioedema. Although published anecdotes have suggested that the risk of anaphylaxis or angioedema attributed to other agents is higher in patients taking an angiotensin-converting-enzyme inhibitor, this has not been firmly established. It is important to remember that the patient population most likely to suffer a stroke is also most likely to be taking an angiotensin-converting-enzyme inhibitor.

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Reference

[The authors respond:] We thank William Chodirker for his informed comments. We recognize the distinction between true IgE-mediated anaphylaxis and non-IgE-mediated anaphylactoid reactions. However, Chodirker is correct that in the discussion section of our article the distinction is blurred. To be clear, we do not believe that these reactions represent true anaphylaxis.

We postulated that our first patient may have had undiagnosed acquired or hereditary angioedema because she had had 8 previous episodes of angioedema of which only 1 was related to taking an angiotensin-converting-enzyme inhibitor. This diagnosis remains speculative.

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We understand that true hereditary or acquired angioedema is resistant to antihistamines and corticosteroids. Chodirker is correct to point out that our treatment was based upon the emergent approach to undiagnosed angioedema that does include antihistamines, steroids and epinephrine. Our empirical regimen appears to work in angioedema associated with tissue plasminogen activator but of course we have no control group with which to properly assess efficacy. Given our experience with our first patient, who ultimately died, we remain committed to treating alteplase-associated angioedema because the regimen is generally safe.

Finally, although we agree that epidemiological evidence (i.e., a good case–control study) is needed to assess the true risk of angioedema with thrombolytic stroke treatment in patients on angiotensin-converting-enzyme inhibitors, we would challenge Chodirker to assess the proposed mechanism for biological plausibility because it is all we have at the moment.

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Treatment of primary insomnia

A major problem with the meta-analysis by Anne Holbrook and colleagues of benzodiazepine use in the treatment of insomnia is that benzodiazepines were considered as a single medication; this class of drugs in fact consists of several compounds with marked differences in pharmacokinetics and side-effect profiles. Patients may be prescribed short-, intermediate- or long-acting compounds. Among other side effects, short-acting benzodiazepines cause daytime anxiety, amnesia and rebound insomnia upon withdrawal, whereas long-acting compounds cause residual sleepiness and cognitive impairments. Because the side effects differ so much from one compound to the next, those of benzodiazepines were not found to differ significantly from those of either a placebo or other insomnia treatments in the meta-analysis, which pooled studies investigating different benzodiazepines. They are nevertheless of prime importance for the clinician who has to choose a single hypnotic.

These side effects, especially the residual sleepiness and cognitive impairments, considerably limit the clinical use of benzodiazepines. As a result, several controlled studies have concluded that zopiclone should be recommended in ambulant or out-patient populations. The effects of hypnotics on breathing during sleep should also be considered. There are several indications that benzodiazepines depress respiration during sleep whereas zopiclone does not. This is important, especially in patients with chronic obstructive pulmonary disease, sleep apnea syndrome and upper airway resistance. Because the side effects differ so much from one compound to the next, those of benzodiazepines were not found to differ significantly from those of either a placebo or other insomnia treatments in the meta-analysis, which pooled studies investigating different benzodiazepines. They are nevertheless of prime importance for the clinician who has to choose a single hypnotic.

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References