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.[1] 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.[2] This variable might affect test results in Canada given that ambient room temperature fluctuates. For the findings of Sievenpiper and collegues to be beneficial globally, comprehensive investigations should be carried out at high and low ambient temperatures.

Subhash C. Arya
Research physician
Centre for Logistical Research and Innovation
New Delhi, India

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[Two of the authors respond:]

We agree with Subhash Arya that ambient temperature during an oral glucose tolerance test might be another important determinant of outcome. However, the findings of Schmidt and coworkers,[1] which form the basis of this suggestion, are complicated by several factors. Their analysis involved pregnant subjects, was observational (temperature was measured, not controlled) and did not differentiate between the effects of acute and chronic ambient temperature. Three earlier studies that investigated differences in blood glucose levels at 2 clinically controlled temperatures (23°C v. 33°C) in nonpregnant subjects are more directly applicable.[2–4] All 3 support the findings of Schmidt and coworkers,[1] demonstrating that an increase in ambient temperature increases 2-h plasma glucose levels after a 75-g oral glucose tolerance test.

To avoid the possibility that changes in ambient temperature might confound our results, the temperature is controlled in our clinic by a thermostat set at 22°C and subjects acclimatize for a minimum of 15 minutes before commencing testing. The blood glucose raising effect of dilution we observed at 30, 45 and 60 minutes and for the area under the curve, therefore, is relevant for this temperature.[5] Whether our observations at 22°C would hold at higher or lower temperatures is unclear. Temperature should not interact with the effect of dilution, provided the temperature is constant for each dilution. There is no direct evidence to suggest that the gastric-emptying mechanism, by which dilution is thought to increase glycemia, is influenced by ambient temperature within normal testing limits, although cold stress might affect gastric emptying.[6]

It would be interesting to explore the interaction between the effects of temperature and dilution on postprandial glycemia in a further study, but such a study likely would not yield practical results. It is probably sufficient to be aware that both of these factors affect the outcome of oral glucose tolerance testing. In this regard, attempts might be considered to standardize ambient temperature and account for its effects when comparing across centres. The same might be considered for dilution when using oral glucose tolerance testing criteria that rely on intermediate time points for diagnosis, as these points, but not 2-h postprandial glucose levels, appear to be sensitive to alterations in dilution.[5]

John L. Sievenpiper
Vladimir Vuksan
Department of Nutritional Sciences
Faculty of Medicine
University of Toronto
Toronto, Ont.

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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-

tients treated for acute thrombotic stroke.[1] 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 CI esterase inhibitor deficiency. Levels of C4 were reported to be normal in this patient, arguing strongly against CI 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.

William B. Chodirker
Allergist and clinical immunologist
London Health Sciences Centre,
University Campus
London, Ont.

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[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[1] 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.

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.

Michael D. Hill
Philip A. Barber
Jennifer Takahashi
Andrew M. Demchuk
Thomas E. Feasby
Alastair M. Buchan
Department of Clinical Neurosciences
University of Calgary
Calgary, Alta.

Reference

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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[1] 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.[2,3] 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.[4–7] This is important, especially in patients with chronic obstructive pulmonary disease, sleep apnea syndrome and upper airway resistance and, to a certain extent, in people who snore. Another clinical indication of zopiclone is its usefulness in the treatment of benzodiazepine dependency.[8–10] Finally, a major advantage of zopiclone is that, unlike most benzodiazepines, it does not modify sleep architecture (most benzodiazepines reduce both slow-wave and REM sleep).[6,11]

I agree with Anne Holbrook and colleagues that nonpharmacological treatments are the treatment of choice for chronic primary insomnia.[1] However, when comparing hypnotics, I believe that zopiclone has several advantages over each benzodiazepine taken separately.

Jacques Montplaisir
Sleep Disorders Centre
Hôpital du Sacré-Cœur de Montréal
Montreal, Que.

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[The authors respond:]

Although Jacques Montplaisir may be correct in his assertion that shorter and longer acting benzodiazepines differ in their profiles of adverse effects on the central nervous system, this was not evident in our systematic review.[1] Many of the studies published on amnesia and rebound insomnia have involved triazolam, a potent benzodiazepine with one of the shortest half-lives of the group. However, these and other cognitive impairment effects have been ascribed to all benzodiazepines.[2,3] We remind readers that no benzodiazepine is reliably short acting in terms of sedation in elderly patients with comorbidity, particularly if doses are not adjusted downward.[4–6] There has been virtually no research on therapeutic strategies for insomnia involving this group of patients, who are arguably the highest per capita users of benzodiazepines and alternatives.

Zopiclone is an interesting nonbenzodiazepine sedative. Unlike Montplaisir, we are not convinced that it is superior in efficacy or safety to all benzodiazepines. Studies involving zopiclone tend to be disabled by the use of suboptimal benzodiazepines for comparison (very-long-acting benzodiazepines are used instead of shorter acting drugs similar to zopiclone), small patient numbers and concerns regarding dose equivalence. Our systematic review of 9 randomized controlled trials including 3

appropriate for meta-analysis did not suggest that zopiclone is superior for sleep.[1] A separate meta-analysis of sleep laboratory studies also noted the paucity of high-quality studies involving zopiclone, but the available studies suggest that it is similar to shorter acting benzodiazepines in efficacy, tolerance and rebound.[7] Several studies have noted that zopiclone has adverse effects on human performance similar to those seen with benzodiazepines.[8–11] Finally, although it represents a lower quality of evidence according to our criteria, we are highly persuaded by the zopiclone manufacturer's own product monograph (monographs are often based on information not available for public scrutiny) that "the pharmacological profile of zopiclone is similar to that of the benzodiazepines."[12]

Anne Holbrook
Renée Labiris
Centre for Evaluation of Medicines
St. Joseph's Hospital
Hamilton, Ont.

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