Closet Hypoglycemia

Irving Robinson, MD; Robert L. Deamer, PharmD; and John G. Prichard, MD
Los Angeles and Ventura, California

An elderly nondiabetic woman was found stuporous and unresponsive at home. In the emergency department, testing revealed that she had a serum glucose of 40 mg/dL (2.2 mmol/L). No underlying metabolic cause could be determined. An inspection of her medications disclosed a professional medication sample bottle labeled as containing a nonsteroidal anti-inflammatory drug (NSAID) that actually contained chlorpropamide tablets.

Drugs, notably sulfonylureas, must be considered as a possible cause of unexplained severe hypoglycemia.

Key words. Hypoglycemia; drug toxicity; sulfonylurea compounds; hypoglycemic agents. (*J Fam Pract 1994; 38:78-79*)

Dispensing of pharmaceutical samples in the office setting is a traditional practice that has received recent attention and criticism in the medical[1,2] and lay[3] press. The following case illustrates an unanticipated complication of drug sample dispensing.

Case Report

An 89-year-old woman was receiving care for the management of hypertension and osteoarthritis. On April 21, 1993, she was found in her home in a stuporous and unresponsive state. The paramedic crew administered one 50-mL ampule of 50% dextrose solution to the patient before transporting her to the hospital. On examination in the emergency department, the patient's serum glucose was found to be 40 mg/dL (2.2 mmol/L). The patient improved dramatically following administration of one additional 50 mL-ampule of 50% dextrose solution.

Once awake, her general and neurological examination was normal except for amnesia for the immediately preceding events. Laboratory and clinical assessment ruled out endocrinopathy, liver disease, and other physiologic causes of hypoglycemia. The patient was hospitalized for 4 days, and required a continuous infusion of a 10% dextrose solution to maintain serum glucose levels between 90 and 120 mg/dL (5.0 to 6.7 mmol/L). She was discharged from the hospital on the 5th day without detectable sequelae.

The patient lived alone and denied having taken any medications other than her usual ones. Her medication included aspirin 325-mg tablets, one half tablet daily; hydrochlorothiazide 25 mg daily; niacin 250 mg twice daily; temazepam 30 mg nightly; quinapril 10 mg twice daily; and etodolac 300 mg three times daily. Her physician recently had prescribed etodolac for osteoarthritis and had given several sample bottles of the drug to her.

Since the hypoglycemic episode was suspected to have been drug induced, each vial of medicine in her possession was carefully inspected when she was admitted to the hospital. A suspiciously large supply of tablets was found in a drug sample bottle labeled as containing etodolac. A search of the product identification tables in the *Physicians' Desk Reference*[4] confirmed that the tablets contained in the bottle were actually chlorpropamide 250-mg tablets, a long-acting oral hypoglycemic agent.

The discovery of chlorpropamide tablets in the etodolac sample bottle was discussed with the patient's personal physician. After some thought and investigation, the source of the chlorpropamide was found. One of the physician's other patients, a diabetic, had returned several etodolac sample bottles after experiencing gastrointestinal side effects from the drug. The physician placed the

Submitted, revised, August 18, 1993.

From the Departments of Family Medicine (I.R., R.L.D.) and Internal Medicine (J.G.P.), Ventura County Medical Center, Ventura, California, and School of Medicine, University of California at Los Angeles (R.L.D., J.G.P.). Requests for reprints should be addressed to Robert L. Deamer, PharmD, Department of Medical Education, Ventura County Medical Center, 3291 Loma Vista Rd, Ventura, CA 93003.

ISSN 0094-3509

bottles back in the sample closet not knowing that his patient had inadvertently returned the particular sample bottle he had been using to store a supply of his chlorpropamide tablets. This sample bottle, along with others, was unknowingly dispensed to our patient.

Discussion

Sulfonylurea drugs have been implicated as the cause in most published reports of severe refractory hypoglycemia, especially incidents involving the elderly. The incidence appears to be related to the duration of action and potency of the particular drug.[5] The highest incidence occurs with the long half-life derivative chlorpropamide and the highly potent glyburide, which produces hypoglycemic episodes with a frequency twice that of glipizide and five times that of tolbutamide.[6]

In these cases, as in ours, the hypoglycemia produced was quite prolonged, requiring intravenous dextrose infusions for several days.

Patient risk factors for severe sulfonylurea-induced hypoglycemia include age greater than 60 years, impaired renal function, poor nutrition, and multidrug therapy. It is important to note that the mortality rate in severe cases approaches 10%.

Physicians should use caution when accepting the return of unused drug samples for subsequent distribution to other patients. This case illustrates the potential hazard of this practice and confirms that unexpected hypoglycemia in the otherwise healthy patient is usually drug induced.

References

1. Morelli D, Koenigsberg MR. Sample medication dispensing in a residency practice. J Fam Pract 1992; 34:42–8.
2. Storrs FJ. Drug samples. A conflict of interest? Arch Dermatol 1988; 124:1283–5.
3. Wilkes MS, Shuchman M. Pitching doctors. The New York Times Magazine 1989 Nov 5:88.
4. Physicians' desk reference. Montvale, NJ: Medical Economics Data, 1993.
5. Seltzer H. Drug-induced hypoglycemia. A review of 1418 cases. Clin Endocrinol Metab North Am 1989; 18:163.
6. Gerich JE. Oral hypoglycemic agents. N Engl J Med 1989; 321: 1231–45.

History of Medicine

Thomas Sydenham, MD (1624–1689): The Father of Clinical Observation

The excellence of the art of medicine does not depend on elegant prescriptions but on observation.[1]

—Thomas Sydenham, MD

All histories of medicine praise Thomas Sydenham's contributions to medicine: some acclaim him the greatest physician of the 17th century, and others call him the greatest physician England ever produced. This essay focuses on Sydenham's role in clinical medicine and his philosophy, methodology, and contributions.

Inspired by Ionian philosophy, Hippocrates abandoned temple medicine for a rational practice that embodied observation at the bedside of the patient, exact recording of the phenomena of disease, reasoning, and accumulating experience. The feudal system that replaced the Greco-Roman era in the 5th century AD discarded the medicine of Hippocrates for supernaturalism and magic, which survived in clinical practice for over 1200 years.[1–11]

The events that again stimulated progress and knowledge in medicine occurred in the Renaissance, which began in Italy in the 15th century. This period was illuminated by the achievements of Vesalius in human anatomy, Fracastoro in infectious disease, Paré in surgery, and Servetus in circulation.

The second event was the change in 17th century England from a decaying feudalistic society to a new socioeconomic structure. Concurrently, there was a revolution in medicine and science: discovery of circulation by Harvey, a philosophy of science by Bacon, disease by Ramazzini, and microscopic revelations by Malpighi and Leeuwenhoek. It was Thomas Sydenham's contributions, however, that truly revolutionized medical practice.

Thomas Sydenham matriculated at Oxford University in 1642, but left shortly thereafter to join the Parliamentary troops fighting the civil war. Four years later, he returned, earned a Bachelor of Medicine degree in 1648, and accepted a fellowship at All Souls' College. He was awarded a licentiate by the College of Physicians in 1663, and the medical doctorate degree by Cambridge University in 1676.

In 1655, Sydenham resigned his fellowship to practice medicine and get married. He soon became aware of the paralysis of his art. The remedy he chose was to practice Hippocratic rational medicine free of Galenic orthodoxy, medievalism, and confusing theories and systems. His philosophy and methodology had its origin in Bacon's *Novum Organum* and in the Hippocratic maxim, "You must go to the bedside. It is there alone you can learn disease." In his treatise "On Dropsy," Sydenham wrote: "The philosophy of medicine consists in working out the history of diseases and to apply the remedies which can dispel them. In this process, experience is the sole guide." Sydenham incorporated his knowledge of the influence of environment, emotion, stress, diet, season of the year, rest, exercise, inherited constitution, and atmospheric corruption with bedside observation and experience to "work out" the history of diseases and remedies. Through this philosophy and methodology, Sydenham successfully terminated the period of stagnancy in medical advancement.[1,2]

Sydenham wrote about disease, not about sick people. This was an original idea, evidenced by his masterly descriptions of the differentiation between gout and rheumatism, scarlet fever and measles, malaria and other fevers, and chorea and St Vitus dance, as well as his descriptions of dysentery, pneumonia, mental diseases, tuberculosis, influenza, trigeminal neuralgia, croup, and syphilis.

Sydenham's image of a disease was ontological: an acute illness develops rapidly with fever, and the action can be violent and quickly ended; a chronic disease reacts slowly and with difficulty in response to harmful agents that act longer; and a seasonal disease, such as pneumonia, appears at a specific time of year, such as winter. Fever, Sydenham wrote, is a property of the blood and a defense mechanism.

In a time of excessive bloodletting, purges, emetics, and loathsome drugs, Sydenham's approach to therapy was practical and sensible. He was an advocate of only the most effective methods in therapy and a believer in "vis medicatrix naturae"

Requests for reprints should be sent to Harry Bloch, MD, 49 Crest Dr, South Orange, NJ 07079.

and in nature's efforts to cleanse the body from disease by means of fever, sweating, looseness, and eruptions. He advised doctors to assist nature by respecting the body's self-healing ability, to proceed slowly, to determine whether therapy has been helpful or injurious, and to promptly discontinue therapy if it has failed. He also emphasized that healing in chronic illness is slow, and that in diseases such as palsy, the patient is too weak to expel noxious matter.

Sydenham's therapy consisted of a carefully regulated diet, fresh air in the sick room, abundant liquids, cooling drinks for fever, iron for anemia, mercurial inunctions for syphilis until the patient salivates freely, cooling air for smallpox, horseback riding for patients with tuberculosis to provide fresh air and exercise, his own laudanum preparation for heart ailments, powdered deer horn (a form of lime) for dysentery, and cinchona bark for malaria.

Sydenham described symptoms as the result of agents producing the disease; accidental symptoms were nature's attempts to cure, and artificial symptoms were incident to the application of therapy.[12–18]

He won many foreign followers, among whom were the "Italian Sydenham," Georgio Baglivi (1668–1706), and Hermann Boerhaave (1668–1738), who always tipped or removed his hat when Sydenham's name was mentioned. Sydenham's influence in the British colonies was evident in the first one-page medical publication (January 1, 1678). It consisted of an extract from Sydenham's *Observations Medical* (1676).[19,20]

When Sydenham died, his remains were buried at St James Church, in Piccadilly, London, where the College of Physicians placed a plaque in 1810, with the legend "A Medical Nobleman for All Times."[1,20] Sydenham's writings, which included diseases that he was the first to record, represented sound common sense and have been read by generations of physicians who value bedside observation, clear and accurate reasoning, experience, and freedom from theories and systems.

Contributed by
Harry Bloch, MD

Acknowledgment

I am grateful to Ann Pasquale, Chief Librarian of the Rare Book Room, the New York Academy of Medicine, for the many volumes on Thomas Sydenham that were made available to me.

References

1. Dewhurst K. Dr. Thomas Sydenham (1624–1689). His life and original writings. London: Wellcome Historical Medical Library, 1966.
2. Robinson V. The story of medicine. New York: Tudor, 1936:315–7.
3. Castiglioni A. A history of medicine. New York: Alfred E. Knopf, 1941:545–50.
4. Withington ET. Medical history. London: Holland Press, 1964.
5. Major RH. A history of medicine. Springfield, Ill: Charles C. Thomas, 1954:524–6.
6. Still GF. The history of pediatrics. London: Dawsons, 1965:276–91.
7. Garrison FH. An introduction to the history of medicine. Philadelphia: WB Saunders, 1929:269–71.
8. Portraits of Thomas Sydenham. Ann Med Hist 1940.
9. Lund FH. Greek medicine. New York: Hoeber, 1936:15–8.
10. Edelstein L. Ancient medicine. Baltimore: Johns Hopkins Press, 1962:455–61.
11. Talbot CH. Medicine in Medieval England. New York: Elsevier, 1967:125–34.
12. Major RH. Classical description of disease. Springfield, Ill: Charles C. Thomas, 1948:194–228.
13. Combrie JD. Selected works of Thomas Sydenham, MD. A short biography and explanatory notes. London: Bale and Danielson, 1922.
14. Latham RG. The life and works of Thomas Sydenham, MD. London: Sydenham Society, 1848.
15. Swan J. The entire works of Thomas Sydenham. London: Corr, 1753.
16. Winslow CEA. The conquest of epidemic disease. Princeton, NJ: Princeton University Press, 1943:161–75.
17. Le Fanu WR. Notable medical books. Indianapolis, Ind: Lilly Research Laboratory, 1976:89.
18. Austin RB. Early American medical imprints, 1668–1820. Washington, DC: Government Printing Office, 1961:133, 199.
19. Bloch H. Thomas Thacher, 1620–1678. First colonial pamphleteer. N Y State J Med 1973;73:700–2.
20. Reisman D. Thomas Sydenham, clinician. Ann Med Hist 1925;7:171–81.