Letter to the editor: “Why isn’t clinical experience with ouabain more widely accepted?”

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TO THE EDITOR: In the article “Why isn’t endogenous ouabain more widely accepted?” (2), Mordecai P. Blaustein refers to Thomas Kuhn in stating that scientists tend to ignore ideas and data that don’t fit their preconceptions and often don’t even read (or digest) articles that fall outside their “comfort zone.” Such a behavior is certainly true for many scientists engaged in research on endogenous ouabain. How else can it be explained that in the many publications on endogenous ouabain, no reference is made to the clinical experience with ouabain in the treatment of heart disease? How else can one claim, ouabain causing heart damage despite well-documented positive clinical experience in the treatment of heart disease with ouabain? How else can one neglect current reports on cardio protection induced by ouabain (12)? How else can one assert that endogenous ouabain raises blood pressure although in clinical experience a reduction of high blood pressure in patients is observed on treatment with ouabain (8, 14, 15)? In addition, ouabain reduces blood pressure in several animal species (5). How else can one claim to be surprised by an antagonistic relationship between digoxin and ouabain when ouabain has been used effectively to treat digitalis intoxication? Corresponding reports are documented as early as 1902. Recent in vitro and in vivo studies confirm this well-known clinical observation (13).

Ouabain has been widely used in Europe, and especially in Germany, to treat heart failure. As early as 1904, a standardized solution of the pure substance was commercialized by E. Merck, Darmstadt and Boehringer Mannheim as “g-Strophanthin Thoms.” This ouabain solution was used both intravenously (4) and orally administered in the treatment of heart diseases. In 1909, the French physician Henri Vaquez introduced the intravenous application of ouabain (“Ouabain-Arnaud”) in France (16, 17). Some medical centers in the United States, too, have used the “French preparations” to treat heart diseases (9).

The database of the German Institute for Medical Documentation and Information records more than 20 orally administered ouabain preparations that were used in Germany after 1950. In 1949 Boehringer Mannheim introduced a version of ouabain formulated as a tablet for sublingual application under the brand name Strophoral. In clinical practice, inconsistent experiences were made with the use of Strophoral, which provoked doubts about the reliability of its absorption. Pharmacological studies led to the development of improved products such as Purostroph Dragees, Alvoral mr, and Strodival mr that all were enteric coated preparations. Strophopem, Strophinos, and Strophocor N were oleopholic solutions for sublingual administration. With these preparations the necessary dosage for reliable therapeutic results were achieved at a considerably lower dosages than with Strophoral. The daily dose of Strophoral often amounted to 20–30 mg ouabain (7); for the Purostrophan enteric-coated tablets, 2–6 mg/day were sufficient (18). The daily dose of Strophoperm with 0.5–1 mg ouabain compared in magnitude with intravenous-administered ouabain (1). After oral and perlingual administration of ouabain preparations, serum concentrations between 0.1 and 0.9 ng/ml have been measured (3, 6).

Until well into the 1970s, total absorption of a drug was considered to be the relevant criterion and not serum concentration. Today drugs such as Aliskiren, whose absorption rate is about 3%, will not be rejected just because the absorption rate is too low. Aliskiren’s therapeutic effects derive from sufficiently high serum concentrations, not from the total amount absorbed. The same is true for drugs like Nisoldipine (5%), Dabigatranetexilat (6.5%), or Ramipril (15%), which have absorption rates comparable to that of ouabain. For ouabain, absorption rates of 10% have been measured (11). Thus, contrary to textbook knowledge handed down over the decades, ouabain in appropriate galenic formulations is suitable for oral administration.

In addition to the uncertainty on the identity of endogenous ouabain (10), the ignorance of the extensive literature on the clinical experience with ouabain certainly contributes to the fact that endogenous ouabain “isn’t more widely accepted.”

DISCLOSURES
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REFERENCES


