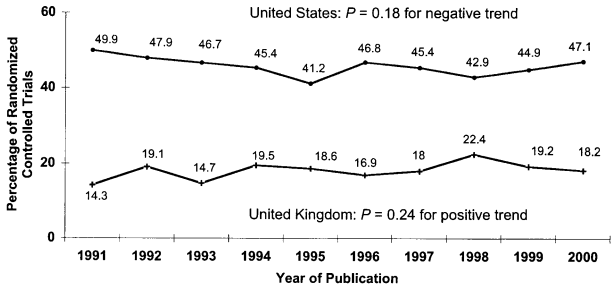

Figure. Publication of randomized controlled trials (percentage of total) from the United States and the United Kingdom (1991 to 2000).

Corporation, College Station, Texas), to determine any changes in the contributions of different countries over time.

From 1991 to 2000, 3500 randomized controlled trials were published in the selected journals. The United States had the most publications (n = 1604 articles [46%]), followed by the United Kingdom (n = 634 articles [18%]) (Table). However, the United States showed a negative trend during this period (Figure), whereas the United Kingdom showed a positive trend, although these trends were not significant. Other countries did not have any significant publication trends over time. Our findings suggest that although research funding in the United States may have decreased somewhat during the last decade, as suggested by the negative trend observed with respect to the United States' contribution of articles to different journal categories (1–3), support for conducting randomized controlled trials has remained fairly constant.

Our findings should be interpreted in the context of the following limitations. Although we selected journals with the highest impact factors, we studied only a small subgroup of general and general internal medicine journals. However, in a study in which all the randomized controlled trials that were published during 1995 to 1999 and were included in the MEDLINE database were searched, the United States' share was 45% (5), which is similar to our recent estimates. In addition, some studies involved a multinational collaboration, and MEDLINE only identifies the affiliation of the corresponding author.

In conclusion, the proportion of U.S. randomized controlled trials published in top general internal medicine journals has decreased somewhat during the past decade, although this decline is not statistically significant.

Mahbubur Rahman, MBBS, MPH
Tsuguya Fukui, MD, MPH
Kyoto University Graduate School of Medicine
Kyoto, Japan

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GRAPEFRUIT AND TONIC: A DEADLY COMBINATION IN A PATIENT WITH THE LONG QT SYNDROME

To the Editor:

We report a 31-year-old woman who was admitted with polydipsia a few weeks after she had received the diagnosis of diabetes based on the presence of hyperglycemia. She had a known asymptomatic long QT syndrome, for which she was taking low-dose atenolol. At age 19 years, she had undergone implantation of a pacemaker because of asymptomatic second-degree atrioventricular block. Her older brother and sister had died of sudden death when they were about 30 years old.

Shortly after admission, she developed frequent convulsive syncopes due to torsade de pointes. Electrolyte level, thyroid function, and glycemia were normal. The QTc interval was 0.58 seconds. Treatment with intravenous magnesium sulfate and metoprolol had no effect on the duration and incidence of torsade de pointes. Overdrive ventricular pacing was not tolerated. Further investigation revealed that she had been drinking excessive amounts of grapefruit juice and quinine-containing tonic water because of her polydipsia. Forty-eight hours after the discontinuation of these drinks, the torsade de pointes disappeared. The QTc interval was 0.45 seconds after 2 days. No arrhythmias were induced with programmed electrical stimulation. However, a cardiac defibrillator was implanted because of her family history of the long QT syndrome. The patient was discharged. She was instructed to take metoprolol (100 mg) once a day, as well as about maintaining an appropriate diabetic diet. She also received a list of products that may prolong the QT interval or induce torsade de pointes.

Torsade de pointes in this patient may have been brought about by the concomitant excessive intake of grapefruit juice containing naringin and tonic water containing quinidine. Quinidine, the optical isomer to quinine, prolongs the QT interval (1). It may also trigger torsade de pointes during, for example, astemizole therapy (2). The inhibitory effect of the flavonoid naringin on the liver cytochrome P450 3A4, which is involved

in the metabolism of quinine, is less well known. Concomitant use of naringin and quinine is associated with increased oral bioavailability (3). However, reports of the effect of naringin on the pharmacokinetics of quinine have been conflicting (4,5). Further information about the concomitant use of both substances in patients with the long QT syndrome is needed since these patients are especially vulnerable to rhythm disorders. Autonomic neuropathy can cause the long QT syndrome in patients with diabetes (6). Beta-blockers have been shown to be efficacious in about 90% of patients, with a significant reduction in rate of sudden death (7). Implantation of a cardiac defibrillator should be considered in high-risk patients. Left stellectomy and overdrive pacing may be useful in patients with bradycardia. Recent therapies that affect the ion channels are being tested. A list of potentially harmful products should be given to patients with the long QT syndrome. Clinical, electrocardiographic, and genetic screening of family members may also be helpful in identifying young adults who are at risk of sudden death.

Kurt Hermans, MD
Dirk Stockman, MD
Frank Van den Branden, MD
Department of Cardiology
Middelheim Hospital
Antwerp, Belgium

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