Editorial

The Need for a Post-Marketing Surveillance Program in Israel

Joshua Shemer MD

Israel Center for Technology Assessment in Health Care, Gertner Institute for Clinical Epidemiology and Health Policy Research, Tel-Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Israel

Key words: drug safety, post-marketing surveillance

IMAJ 1999;1:98–99

Any drug, no matter how trivial its therapeutic actions, has the potential to do harm. It is not uncommon for new dangers to be discovered after the drug has been marketed; in fact 51% of approved drugs have serious adverse effects not detected prior to approval [1].

The total time of drug development from the time of filing application for an investigational new drug to final approval averages 8–9 years. During this time extensive clinical trials are conducted and risk-benefit analysis is performed [2]. The results of these studies are being evaluated by the FDA prior to market authorization. The result of this process has been an increase in the inherent tension that exists between the FDA, which is motivated to protect the public health, and the multinational pharmaceutical companies, which are motivated to market effective and profitable drug products. In addition, medical practitioners and some patient groups have criticized the FDA for delaying the approval of new drugs. In this climate, the FDA has the difficult task of balancing the requirement to ensure the safety of new drugs with the needs of society for useful medications to be made available in a timely manner [3].

Even large, well-designed clinical trials that are conducted to gain pre-market approval cannot uncover every problem that may come to light once a product is widely used. A new drug application typically includes safety data on several hundred to several thousand patients. If an adverse event occurs in one in 5,000 or 10,000 users, it could be missed in clinical trials but poses a serious safety problem when released to the market. Hence, as thoroughly reviewed by Shani in this issue [4], the need for a post-marketing surveillance program is of the utmost importance.

In response to voluntary reports from physicians, other health care professionals and patients, the FDA has issued warnings, made labeling changes, and ordered product withdrawals that have prevented patient deaths and suffering. In 1998, the FDA removed five pharmaceuticals from the market because of unexpected adverse events [5]. Among these were fenfluramine and dexfenfluramine for weight loss, which were reported to cause cardiac valvular disease. The antihistamine terfenadine was found to cause cardiac arrhythmias when co-administered with an inhibitor of the hepatic cytochrome p450 enzyme system, such as erythromycin or ketoconazole. The calcium channel blocker mibefradil for the treatment of hypertension was withdrawn because of potentially harmful interactions with a large number of other drugs due to inhibition of the cytochrome p450 enzyme system. The nonsteroidal anti-inflammatory drug bromofenac was withdrawn from the market by the manufacturer after the FDA received 20 reports of serious adverse hepatotoxic events.

Each year, prescription drugs injure 1.5 million people so severely that they require hospitalization, and about 100,000 of them die, making prescription drugs a leading cause of death in the U.S. [5]. The cost associated with drug-related morbidity and mortality is estimated to be more than 100 billion dollars annually in the USA [7].

At the present time, with the FDA required by congress to shorten its review period of applications for the approval of new drugs, a public outcry is being heard to reexamine the adequacy of the existing system for monitoring and enhancing the safety of approved drugs.

Most of the FDA's work centers on evaluating new drug applications, and a small percentage of its workforce is focused on monitoring the safety of marketed drugs. Suggestions have been made to separate the powers of the FDA and to establish an independent drug safety board that will concentrate exclusively on post-marketing surveillance and monitoring of adverse drug events [8–10].

The case study reported in this issue by Weiss et al. [11] demonstrates that Israel is no different from any other developed country, and reveals the importance of a national post-marketing surveillance program. The dilemma faced by the decision-makers at the Ministry of Health in such cases is what intervention should be taken: on the one hand, the public's health is our principal concern; on the other, an obvious correlation between the adverse event and the drug cannot be proven. Hence, there is a need for a rational risk-benefit analysis to be performed in order to decide on the correct mode of action. Informing the public of the event, its investigation,

and the interventions decided upon is another important issue (particularly in light of the Patients' Rights Act).

To conclude, it appears that the way to deal with the safety of drugs is the "dynamic regulation" approach. This means that a new drug may be approved for marketing, based solely on scientific data gathered from randomized controlled clinical studies. Once it has been approved the drug should be continuously monitored so that every reported event will be evaluated and an intervention will be carried out, if necessary. A post-marketing surveillance system should provide quantitative data necessary for the proper therapeutic and regulatory decision. These data must be adequate for measuring both the beneficial effects and the associated risks of drugs used in actual practice, and should provide information that can be used to determine the value of these drugs. A post-marketing surveillance system must involve the drug-regulatory agency, physicians, nurses, pharmacists, pharmaceutical manufacturers, health insurers, legislators, and the general public. Israel must strengthen its post-marketing surveillance system in order to improve the patients' drug therapy. As stated above, a good post-marketing surveillance system can reduce morbidity and mortality and save unnecessary health expenditures.

References

1. U.S. General Accounting Office. FDA drug review: post-approval risks, 1976–85. U.S. General Accounting Office (GAO–PEMD 90–5), Washington DC, 1990.
2. DiMasi JA, Seibring MA, Lasagna L. New drug development in the United States from 1963 to 1992. *Clin Pharmacol Ther* 1994;55:609–22.
3. Avron J. Putting adverse drug events into perspective. *JAMA* 1997;277:341–2.
4. Shani S. Post-marketing surveillance in Israel and adverse drug reactions [review]. *IMAJ* 1999;1:117–19.
5. Friedman MA, Woodcock J, Lumpkin MM, Shuren JE, Hass AE, Thompson LJ. The safety of newly approved medicines — do recent market removals mean there is a problem? *JAMA* 1999;281:1728–34.
6. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;279:1200–5.
7. Johnson JA, Bootman JL. Drug related morbidity and mortality: a cost of illness model. *Arch Intern Med* 1995;155:1949–56.
8. Kleinke JD, Gottlieb S. Is the FDA approving drugs too fast? *Br Med J* 1998;317:899.
9. Moore TJ, Pasty BM, Furberg CD. Time to act on drug safety. *JAMA* 1998;279:1571–3.
10. Wood AJ, Stein CM, Woolsley R. Making medicines safer — the need for an independent drug safety board. *N Engl J Med* 1998;339:1851–4.
11. Weiss P, Mouallem M, Bruck R, Hassin D, Tanay A, Brickman CM, Farfel Z, Bar-Meir S. Nimesulide-induced hepatitis and acute liver failure. *IMAJ* 1999;1:89–91.

Correspondence: Dr. J. Shemer, Director, Israel Center for Technology Assessment in Health Care, Gertner Institute for Clinical Epidemiology and Health Policy, Tel-Hashomer 52621, Israel. Tel: (972-3) 530 3278; Fax: (972-3) 635 4136; email: trqshemer@matat.health.gov.il

Capsule

Vitamin C intake

Recommendations for vitamin C intake are under revision by the Food and Nutrition Board of the National Academy of Sciences. Since 1989 when the last recommended dietary allowance (RDA) of 60 mg was published, extensive biochemical, molecular, epidemiologic, and clinical data have become available. New recommendations can be based on the following nine criteria: dietary availability, steady-state concentrations in plasma in relationship to dose, steady-state concentrations in tissues in relationship to dose, bioavailability, urine excretion, adverse effects, biochemical and molecular function in relationship to vitamin concentration, direct beneficial effects and epidemiologic observations in relationship to dose, and prevention of deficiency. These criteria were applied to the Food and Nutrition Board's new guidelines, the Dietary Reference Intakes, which include four reference values. The estimated average requirement (EAR) is the amount of nutrient estimated to meet the requirement of half the healthy individuals in a life-stage and gender group. Based on an EAR of 100 mg per day of vitamin C, the RDA is proposed to be 120 mg/day. If the EAR cannot be determined, an adequate intake (AI) amount is recommended instead of an RDA. The AI was estimated to be either 200 mg/day from 5 servings of fruits and vegetables, or 100 mg/day of vitamin C to prevent deficiency with a margin of safety. The final classification, the tolerable upper intake level, is the highest daily level of nutrient intake that does not pose risk or adverse health effects to almost all individuals in the population. This amount is proposed to be less than 1 g of vitamin C daily. Physicians can tell patients that 5 servings of fruit and vegtetables per day may be beneficial in preventing cancer and providing sufficient vitamin C intake in healthy people, and that 1 g or more of vitamin C may have adverse consequences in some people.

JAMA 1999;281:7475