



Tragic Consequences of Inadequate Health Technology Assessment

Health technology assessment is a scientific effort to determine the extent to which and under what conditions a specific technology is safe, efficacious, and effective. It has become crucial for all countries and represents a significant challenge to public health (1). In most countries, the Ministry of Health (MoH) has the authority to regulate drugs, which must undergo a rigorous, comprehensive process before their marketing, sale, and use are permitted. Similar regulating processes exist in most countries for medical devices, but are less stringent, and this has already had tragic consequences. In the 1970s, the Dalton shield – an intrauterine birth control device – was introduced in the USA without rigorous testing. The unwanted pregnancy rate was high in women who used it and the side effects were common, mainly pelvic inflammations and uterine perforations (2). Introduction of new surgical procedures only requires a formal regulatory process if it concerns implanting devices in the body for 30 days or more, e.g., implantations of prosthetic heart valves or artificial joints. This may cause rapid diffusion of such procedures without adequate scientific evaluation (3). Interestingly, manufactured baby foods are also not subjected to rigorous testing. Recent news from Israel indicates that this also may have tragic consequences. In early November 2003, three infants with severe, non-traumatic brain damage were admitted consecutively to a Children's Medical Center. Since this represented an increase of such cases, after the admission of the third infant, the Center informed the MoH, whose investigation revealed that since June 2003 a total of 13 infants had been admitted to various hospitals with a similar clinical picture – restlessness, vomiting, diarrhea, apathy, arrhythmias, and convulsions. Two infants died in a coma, whereas in a few others the brain damage was irreversible and one of them eventually died. Common to all affected infants was the fact that they were not breast-fed but received a non-dairy, soybean baby formula manufactured by *Humana*, a German firm specializing in baby food (Everswinkel, near Duesseldorf) and marketed in Israel under the name of *Remedia*. The clinical picture pointed to a vitamin B1 (thiamine) deficiency, ie, the beriberi disease, now almost non-existent in developed countries. This was reinforced after a 6 months old baby, who had been vomiting severely for more than a week, had eye spasms, and was unable to focus its gaze, recovered completely on a 14-day parenteral

therapy with vitamin B1, even before the results of blood test were obtained. Laboratory investigations confirmed that the product indeed lacked vitamin B1, which is essential for the development of the central nervous system; signs and symptoms of its absence from food may appear in infants within 2 weeks. In an effort to prevent irreparable damage, the MoH directed hospitals to inject vitamin B1 to all infants showing symptoms of the beriberi disease. *Remedia* was removed from the shelves and the public was warned about its danger. The New York Municipality and the World Health Organization also issued warnings against the product's use to those who might have purchased it while on a visit to Israel. The MoH asked all parents whose children were fed soy-based *Remedia* baby formula during recent months to bring these infants to primary care clinics for doses of vitamin B1. The assessment is that about 5,000 children consumed this product during the recent months.

Humana accepted full responsibility for the tragic events. Until the beginning of 2003, their product contained 700-800 µg of vitamin B1 per 100 g, whereas the international standard was only 385 µg. It was appropriate for infants up to one year of age. In March/April 2003, the company decided to reduce the dosage to the international standard, and at the same time to manufacture two new products: one for babies younger than 6 months and the other for those between 6 and 12 months of age. However, miscalculations led to a too low dosage (29-37 µg) of Vitamin B1 in the product line for the Israeli market, which was kept separate due to the observance of the Jewish religious law (Kashruth). The company intended to eventually use the new formula in the other product lines as well. However, the testing of the product was not completed and the labels on the two new products still showed the previous, single product vitamin B1 content. In fact, *Humana* was not aware of the error until news started to arrive from Israel. *Remedia* (the Israeli importer and marketer) had been informed about the change in the product, but not about the reduction of the vitamin B1 content in the two new products. *Remedia* relied on the manufacturer and did not report the change to the MoH, which in 2000 approved the use of the former product.

After these events, the Israeli Minister of Health introduced a new regulation requiring health technol-

ogy assessment for baby food, similarly to pharmaceuticals, and called upon his colleagues in other countries to reconsider international regulations for mandatory testing, thus preventing further tragedies. However, senior MoH officials thought that this was not feasible in Israel due to the lack of resources.

Tragedies involving inadequacies of health care systems occur sporadically in all countries. In France, patients with hemophilia were given HIV contaminated blood in 1984. Another tragedy occurred in the United Kingdom when two surgeons in Bristol had a 60% mortality rate for pediatric cardiac surgeries in the 1988-1995 period, whereas the national mortality rate for these procedures was 15% (4). Another tragedy happened in Croatia with the unexpected deaths of 23 hemodialysis patients in a single week, probably caused by an intravascular release of a substrate from two types of Baxter dialyzers (5). The discovery in Israel, towards the end of 2003, of the lack of the vital vitamin B1 in a milk substitute, which caused deaths of three babies and the hospitalization of at least 10 others, shocked the country and established itself as its worst-ever public health tragedy.

The death of a child is an unspeakable tragedy, and even more so when the loss is preventable. In the US, child death review teams provide a well-organized mechanism investigating unexplained deaths of children by looking for patterns and hidden causes. These multidisciplinary groups meet on a regular basis to review child deaths in their area. All participants sign a confidentiality agreement and are provided with the identifying data about each death and the institutional records. Since the first team was founded in Los Angeles (CA) 20 years ago, 200 teams have been

established throughout the US and the world. Unfortunately, Israel lacks such a systematic organization of review teams. Could it have discovered the lack of vitamin B1 in the baby formula after the death of the first infant thus preventing the death of two babies and illness in many more? Following the tragedy, the National Council of Pediatrics intends to study the US model and the possibility of its implementation in Israel.

One hopes that in the aftermath of such tragedies, more people of authority will consider the place and importance of health technology assessment and of quality of care improvement activities and will rigorously promote their introduction into health care systems.

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References

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