Commentary

Gadopentetate Dimeglumine: Reassessment of the Clinical Research Process

Stephen A. Kieffer[1]

> Every known physiologically active exogenous agent also possesses an adverse consequence profile, components of which can remain hidden until the drug is in general marketing and used in a broader population than experienced in the preapproval trials [1].

The report in this issue of the *AJNR* by Tishler and Hoffman [2] of an anaphylactoid reaction to the IV administration of gadopentetate dimeglumine reminds us of the truism that no drug is without side effects and that the benefits derived from the use of an exogenous agent always must be assessed in the light of the risks entailed. Since 1962, United States law has required an extensive formal evaluation and testing process before any new drug is released by the Food and Drug Administration (FDA) for prescription by physicians. FDA approval indicates that the therapeutic benefits of the agent under consideration appear to outweigh the estimated potential risks. In a recent review of all the clinical trials on gadopentetate dimeglumine in the United States (1068 patients examined at multiple centers) completed before this agent was approved by the FDA, Goldstein et al. [3] found that 213 patients had experienced one or more adverse reactions, a prevalence of 20%. Most of these reactions were minor and short-lived. They included headache (7%), a sense of coldness at the injection site (4%), and nausea (2%). Four patients had convulsions, but three of these had a history of seizures. Notably, no anaphylactoid or pseudoallergic severe multiorgan system reactions occurred. On the basis of this experience, gadopentetate dimeglumine was approved by the FDA in June 1988 as an acceptable contrast agent for IV administration in conjunction with MR imaging.

Preapproval testing is both lengthy and complex, assessing both efficacy and safety [4]. The FDA's evaluations of the results of preapproval testing, although frequently the target of vigorous (and often justified) criticism from the scientific community because of their excessive length, have proved effective in identifying and eliminating potential drugs that are markedly toxic [5]. However, preapproval testing is an inherently limited process, involving a relatively small sample of the population of potential users of the agent and conducted under controlled conditions that actually limit the extent of risk assessment [1].

Once a drug has been approved by the FDA, it is used by many more patients and under conditions much less controlled than those that prevailed during the preapproval clinical trials. It therefore is not surprising that adverse reactions not identified in preapproval testing can occur in the much larger and far less controlled postapproval environment. Such clearly has been the case with gadopentetate dimeglumine. Tishler and Hoffman [2] indicate that besides the patient described in their report, four additional cases of anaphylactoid reaction to this contrast agent had been reported to its manufacturers by April 1, 1990.

Is this story unique or unusual? Not particularly, according to a current report from the Program Evaluation and Methodology Division of the General Accounting Office of the United States Government [5]. During the decade from 1976 through 1985, 198 drugs were approved by the FDA for which data collected after their approval were available. Of these 198, postapproval reports of adverse reactions sufficiently serious to lead to hospitalization, increase in length of

This article is a commentary on the preceding article by Tishler and Hoffman.

[1] SUNY Health Science Center at Syracuse, 750 E. Adams St., Syracuse, NY 13210. Address reprint requests to S. A. Kieffer.

AJNR 11:1168–1169, November/December 1990 0195–6108/90/1106–1168

hospitalization, severe or permanent disability, or death were received by the FDA for 102 (52%). Sixteen of the 198 agents were radiopharmaceuticals, a term the FDA uses to include both radioactive diagnostic agents and radiopaque contrast agents; in five (31%) of these, postapproval reports of serious adverse reactions resulted in substantial changes in labeling. Four of the five were low-osmolality iodinated contrast agents. The changes required in their product inserts included precautions and contraindications mainly related to the occurrence of convulsions when the agents were administered intrathecally and warnings emphasizing the need to limit the dose injected to the lowest possible amount.

As a senior official of the FDA's Office of Drug Evaluation has noted, regulatory decision making often occurs in an environment of uncertainty [1]. That no anaphylactoid reactions occurred after intravascular administration of gadopentetate dimeglumine during the preapproval clinical trials is neither unusual nor surprising, given the inherently limited nature of such clinical trials. Viewed from the perspective of all FDA evaluations and approvals of new drugs tested during the past 15 years, serious risks identified after approval of new drugs have been reasonably common. This does not diminish the seriousness of the event described by Tishler and Hoffman and acknowledged by the manufacturer to have occurred in at least four other individuals. It is probably too early to attempt to determine the true frequency of anaphylactoid reactions associated with administration of gadopentetate dimeglumine. Nevertheless, it is important to realize that this agent is not innocuous and therefore to observe proper precautions. The admonition of Tishler and Hoffman that personnel be trained in early recognition of serious life-threatening reactions and in proper application of appropriate resuscitation measures should not go unheeded.

REFERENCES

1. Nelson RC. Drug safety, pharmacoepidemiology, and regulatory decision making. *Drug Intell Clin Pharm* **1988**;22:336–344
2. Tishler S, Hoffman JC Jr. Anaphylactoid reactions to IV gadopentetate dimeglumine. *AJNR* **1990**;11:1167
3. Goldstein HA, Kashanian FK, Blumetti RF, Holyoak WL, Hugo FP, Blumenfield DM. Safety assessment of gadopentetate dimeglumine in United States clinical trials. *Radiology* **1990**;174:17–23
4. Kieffer SA. Gadopentetate dimeglumine: observations on the clinical research process (editorial). *Radiology* **1990**;174:7–8
5. *FDA drug review: postapproval risks 1976–1985* (GAO/PEMD-90-15). Washington DC: United States General Accounting Office, April **1990**