The Aprotinin Story: Lessons in Drug Regulation and Safety

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Issues of drug regulation and safety are a familiar concern within the pharmaceutical industry and often do not emerge until several years after a drug has been on the market. The antifibrinolytic drug aprotinin (Trasylol) was developed by Bayer Pharmaceuticals and approved to prevent excessive bleeding in patients undergoing coronary artery bypass grafting surgery. After several years of widespread use of the drug in cardiac procedures, two observational studies demonstrated a risk of aprotinin for serious complications such as renal failure and myocardial infarction. These observations led to a prolonged review of the drug’s safety label by the Food and Drug Administration and to the revelation that Bayer had withheld the results of a privately commissioned observational study which demonstrated these reported complications. This essay highlights the ethical issues raised by the aprotinin saga and discusses the importance of transparency, honesty, and clinical equipoise in drug regulation and safety.

Timeline
On December 30, 1993, the Food and Drug Administration (FDA) announced its approval of the antifibrinolytic agent, aprotinin, developed by Bayer Pharmaceuticals and marketed under the trade name Trasylol for use in cardiac surgery. Antifibrinolytics have long been a mainstay of treatment to prevent excessive bleeding, a frequent cause of morbidity and mortality in patients undergoing on-pump coronary artery bypass grafting (CABG) and other cardiac procedures. Traditional antifibrinolytic agents, including aminocaproic acid (ACA) and tranexamic acid (TXA), often take the form of lysine analogues that prevent bleeding by interfering with the activation of plasminogen to plasmin, a molecule responsible for the degradation of fibrin clots. Aprotinin is unique in that it promotes clotting by inhibition of serine proteases, including plasmin, thereby preventing the degradation of the plasma proteins comprising fibrin clots.

The initial FDA approval was based primarily on two randomized, placebo-controlled clinical trials. One study reported that 77% of patients who received no bleeding prevention therapy required at least one transfusion during or after the operative procedure; among patients who had received aprotinin, only 42% required the administration of blood products. The second study showed similar results. However, the authors also noted the possibility of allergic reaction after chronic usage, as well as incidents of kidney toxicity. Although these adverse effects were sufficiently rare and manageable to permit drug approval, aprotinin was recommended for use primarily in high risk patients.

In the years following its approval, aprotinin gained acceptance into the practice of cardiac surgery. Over 70 studies were conducted to establish and confirm the efficacy of aprotinin by measuring the blood product transfusion requirements of patients undergoing cardiac bypass procedures, with or without aprotinin. A placebo-controlled, double-blind study conducted by Bidstrup et al., for example, demonstrated a significant reduction in blood units required in a high dose aprotinin group following cardiopulmonary bypass. While numerous studies such as this confirmed its efficacy, little hint of the risk of aprotinin was found beyond the initially reported side effects. This was due in large part to the fact that the primary endpoints of the majority of these studies, including that conducted by Bidstrup et al., were transfusion requirements, and the studies were frequently not designed or powered to detect mortality benefit or specific adverse outcomes. While donor blood requirements may be used as an indicator of blood loss, these studies failed to address ‘patient important outcomes’ such as morbidity or mortality.

By 1998, the FDA had expanded the indications for aprotinin use to all CABG patients and its use burgeoned as it became the mainstay of bleeding prevention therapy in cardiac surgery. This was aided largely by its...
newly expanded recommendation, as well as a lack of other drugs indicated for this purpose, as the lysine analogue antifibrinolytics such as TXA were initially developed to prevent bleeding in other procedures and conditions. For several years, the risk of anaphylactic reaction with repeated administration remained one of the only risks identified with aprotinin use.

The first study to raise concerns regarding the safety of aprotinin was conducted by Karkouti et al at the University of Toronto, and was published online ahead of print in Transfusion on January 20, 2006. This observational study employed a method known as propensity scoring to compare risk-variable patients who received aprotinin or tranexamic acid. Propensity scoring is a statistical technique used to control for selection bias in observational studies where treatment allocation is not random, and involves determining the probability, or propensity score, of receiving a particular treatment based on a number of background variables, or covariates, which may plausibly influence treatment assignment. While aprotinin and TXA were found to be quite similar in effectiveness with respect to transfusion requirements, the former was associated with a statistically significant increase in renal dysfunction within the first postoperative week, sometimes requiring dialysis. On January 26, 2006, a similar study conducted by Mangano et al. was published in the New England Journal of Medicine. This multi-centre observational study examined nearly 4500 patients who were administered either aprotinin, aminocaproic acid, tranexamic acid, or no treatment. Through propensity scoring and multivariate analysis, they found that aprotinin was associated with a statistically significant increase in renal dysfunction within the first postoperative week, sometimes requiring dialysis. On January 26, 2006, a similar study conducted by Mangano et al. was published in the New England Journal of Medicine. This multi-centre observational study examined nearly 4500 patients who were administered either aprotinin, aminocaproic acid, tranexamic acid, or no treatment. Through propensity scoring and multivariate analysis, they found that aprotinin was associated with a statistically significant increase in renal dysfunction within the first postoperative week, sometimes requiring dialysis. 

A subsequent follow-up study by Mangano et al. also demonstrated increased risk of long-term mortality associated with aprotinin. These two studies prompted the FDA to initiate a year-long review of the safety of aprotinin, and to convene a meeting of its Cardiovascular and Renal Drugs Advisory Commission on September 21, 2006. The FDA chose neither to amend the label on aprotinin nor to issue any additional safety warnings surrounding potential adverse effects. The primary outcome of the meeting was a reiteration of the initial recommendation that aprotinin be used only in high-risk patients. In defending their decision, FDA committee representatives cited issues of transparency related to an unwillingness to release data on the part of Mangano et al. Mangano responded in a letter to NEJM, indicating that although their data release was initially offered with restrictions related to patient confidentiality and independent analysis, it was eventually offered without restriction prior to the committee meeting and following a lengthy delay in acknowledgment of their data or requests by the FDA. He further indicated that, despite repeated requests, the FDA informed him that a review of his data was unnecessary at that point. Six days following adjournment of the meetings, however, Bayer released the troubling results of an observational study it had commissioned. These findings demonstrated that the use of aprotinin led to an increase in kidney damage, congestive heart failure, stroke, and mortality, and quickly triggered serious safety warnings with respect to the drug.

Following the revelations regarding the safety of aprotinin, many sought to determine what had gone wrong. What they found, however, was even more disturbing than what had already transpired and raised serious issues with respect to manufacturer transparency and deception regarding adverse drug effects. Bayer hired a private contract research team to conduct their observational study on the postoperative complications of aprotinin use, and their findings were similar to those of Mangano et al. Further investigation revealed that Bayer officials were given the preliminary results before the FDA review meetings, yet neither the manufacturer nor the private contract team had shared this information with the regulatory body. They explained that an internal mistake resulted in the delayed release of this information. However, investigation into the body of evidence which initially supported the efficacy of aprotinin revealed that Bayer repeatedly funded numerous small trials which showed the drug to be
effective, but were underpowered to show any rare but serious adverse effects. Meta-analysis later showed that on average these trials referenced only 20% of the preceding reports; only 15% referenced the largest trial, which is considered to be central to the evidence surrounding aprotinin.  

**Ethical Analysis**

The aprotinin case serves to highlight numerous ethical issues with drug regulation and safety as they pertain to the pharmaceutical industry. While public interest and patient safety should be central priorities in all healthcare activities, these can be overlooked or ignored by pharmaceutical companies in favor of drug marketing. However, in this instance, ethical issues are raised not only by Bayer’s actions, but also by those of the FDA and the researchers who sounded the alarm.

**FDA:** According to Mangano, the FDA did not respond to his repeated requests for data review prior to upholding the aprotinin label, citing it was unnecessary. In his response to the FDA’s decision, Mangano stated, “The FDA and its Advisory Committee should take a conservative, protective stance when independent evidence regarding drug safety presents itself. Instead, they appear to be protecting the drug rather than the patient.”

While ethical discussion centered on drug regulation most often focuses on the behaviors of pharmaceutical companies, the aforementioned interactions between Mangano and the FDA call into question the priorities of the regulating body as well. While the FDA did request the data from the Mangano study upon convening its Advisory Commission, it appears as if the FDA did not make every effort to obtain the data via discussion with Mangano before judging the safety of the drug. This raises questions as to the efforts of the FDA and the nature of the influence of pharmaceutical companies on their regulatory body.

**Mangano:** While the researcher did offer the original study data to the FDA, there appeared to be initial resistance to do so in that data release was contingent upon several restrictions including patient confidentiality and independent data analysis. This raises the issue of transparency in research, and the situations in which researchers should be encouraged or obligated to share their data and their analytical methods. Methodological transparency is of particular importance in observational studies where treatment allocation is not randomly assigned and certain analytical strategies are required in order to minimize known biases and approach a true evaluation of effect. Often these are the only means by which critical drug safety issues can be evaluated. Thus transparency becomes a central value in research ethics. However, the concept of transparency itself raises further ethical issues, as the obligation the release individual-level data may conflict with the values of privacy and anonymity.

**Bayer:** Bayer faces the serious charge of withholding information garnered from a privately conducted study at the time of the FDA commission. This goes beyond the concept of transparency and encroaches on honesty, which must undoubtedly be a central value in all research activities. It has become clear that Bayer became aware of at least the preliminary results of the study, yet they did not disclose this information to the FDA Advisory Commission in a timely manner. Drug safety analyses are often an issue because we rely on pharmaceutical companies to fund the studies necessary to assess safety; however, when they have a vested interest in the lucrative success of their product, it is difficult to expect them to fund or disclose the results of studies that might discredit their product or jeopardize its success.

Finally, and most subtly, Bayer’s investigation of the effectiveness of aprotinin remains in stark contrast with the principle of clinical equipoise. This principle states that randomized control trials can only be conducted ethically when true disagreement exists as to the effectiveness of one treatment compared to another. In placebo-controlled studies, it is only ethical to administer no treatment (or a placebo) when no proven treatment exists. Bayer continued to fund placebo-controlled RCTs despite the previous literature supporting aprotinin as an effective treatment for decreasing transfusion requirements. In hindsight, this appears to have been done in order to build the body of evidence supporting this therapy, and to continue to show effectiveness without being
able to identify adverse effects associated with its administration. These studies, while sufficiently powered to detect significance of efficacy, were for the most part too small to have a high likelihood of showing serious and rare side effects. These actions further contributed to the skewed view of aprotinin held by both the public and the medical community, and to its longtime use despite its dangers.

Conclusion

The protracted length of time between the approval of aprotinin for the prevention of excessive bleeding during coronary artery bypass grafting and the revelation of drug safety concerns indicates a need to refine the process of drug safety review. The ethical issues highlighted by the actions of Bayer Pharmaceuticals, the Food and Drug Administration, and the drug researchers indicate that drug safety is not influenced solely by the philosophies of pharmaceutical corporations, but instead it involves complex political and procedural interactions between the pharmaceutical companies, the regulating body, and drug investigators. We have indicated a fundamental requirement for transparency as it pertains to all studies assessing drug safety, particularly on the part of the pharmaceutical companies. As observational studies are often the only means by which we can assess long-term drug safety, it is also important that they be transparent and sufficiently powered to detect long term morbidity and mortality. While the aprotinin saga represents a very recent example, other drugs including flecainide acetate (Tambocor) and rosiglitazone (Avandia) have raised similar issues in the past decade. Major changes are required to refine the evaluation and monitoring of pharmaceutical products following regulatory approval and widespread use. These activities are critical to treatment effectiveness and patient safety.

References