Moments in Surgery

Fifty years ago

Henry Gans, MD, FACS, *Palm City, FL*

In 1960, whenever we worked late at night, George Schimert, a surgical resident on the cardiac surgery service at the University of Minnesota Hospitals in 1960, and I would meet for the free late-night supper for residents on call. At this meal, we would discuss current events and, of course, our own work. That is how he found out about epsilon aminocaproic acid (EACA). I had told him that I had just received a shipment of this new experimental drug from Merck that was supposed to be effective in the treatment of bleeding caused by fibrinolysis. As far as we knew, this condition occurred only rarely.

In June, George called one night to ask me for a sample of the new experimental drug.

"What do you intend to use it for?" I asked.

He said he wanted to try it on a 37-year-old clergyman who had been operated on that morning to replace his aortic valve with a bicuspid prothesis. At that point, the patient was still bleeding, so the surgeons could not close his chest.

"How long was he on cardiopulmonary bypass?"

"Two hours and 9 min. Since then, we have given him everything under the sun; Mephyton (Aton Pharma Inc., Lawrenceville, NJ), polybrene, calcium gluconate, fibrinogen, platelets, low molecular dextran, and so far, since surgery, some 10 h ago, he has received 56 units of blood. So why not try that new medication of yours?"

"Very well, George! I'll be over as fast as I can to draw blood samples before giving him the drug."

The medicine he called about, EACA, which was a synthetic amino acid developed by Okimoto in Japan (in 1951), supposedly had a pronounced antifibrinolytic effect. Sol Sherry and his group in St. Louis, MO, had just reported on it in the *Journal of Biochemistry*,[1] showing its effectiveness and fast action in inhibiting plasminogen activator activity irreversibly. I had mentioned this to George when I had told him that I was looking for suitable candidates for this new, still untested treatment. Anxious to find out how effective it was, I rushed to the hospital. In the operating room, I found the anesthetized patient with his chest wide open and oozing all over. I saw no evidence of any clotting.

After obtaining blood samples and drawing up a vial of EACA, I injected the solution slowly into the venous line. Within a few minutes, the bleeding stopped. Clots began to form that finally allowed the surgeons to close the patient's chest.[2]

No words can do justice to the enormous excitement we all felt when the bleeding stopped shortly after injecting the drug. As incredible as it seemed, here was a patient who had bled all day, despite every known measure, had lost 56 units of blood, but he stopped bleeding almost immediately after receiving this new medication. This incident was a startling and dramatic demonstration of its effectiveness in stopping an uncontrollable and potentially life-threatening hemorrhage.

When I checked the literature, I found that 2 years earlier, Kurt von Kaulla, a hematologist at the University of Colorado, and Henry Swan, a pioneer cardiac surgeon from Denver, CO, had shown that some of their patients developed fibrinolytic activity during open-heart surgery. Our case exhibited a greatly enhanced fibrinolytic activity, as the blood samples I had collected clearly demonstrated, and indicated that this activity could cause a prolonged and potentially life-threatening hemorrhage.

The next day, Dr Walton C. Lillehei, the patient's surgeon, asked me for some of this new medication and wanted to know when he should give it. I mentioned that Merck had sent it with the understanding that we would study it in every case where we used it. In this way, we could evaluate its effectiveness.

"Would you mind," I asked him, "if we studied your patients during open-heart surgery to evaluate its effect?"

Walton said he would be delighted if we did, provided the new medication would be available for his patients. I mentioned that it was a new drug and

Accepted for publication October 6, 2009.

Reprint requests: Henry Gans, MD, FACS, 4450 SW Thistle Terrace, Palm City, FL 34990. E-mail: gans@gate.net.

Surgery 2010;148:162-3.

0039-6060/$ - see front matter

doi:10.1016/j.surg.2009.10.029

that as far as I knew, no one had used it before for that purpose. As for when to give it, I decided that, if necessary, the patient should get it before any anticipated changes develop, because once the plasminogen activator is released, it induces other clotting abnormalities that fail to respond to the drug. Yet, miraculously, the current case had reacted dramatically to its injection some 10 h after surgery. Fortunately for the patient, and for us, he had received for the last 10 h some 5–6 units of blood per hour, so that he had undergone a continuous, massive blood replacement. This, I believe, explained his favorable response to EACA. Under normal circumstances, once the plasminogen activator activity has had time to act—by breaking down factors V, VII, VIII, and fibrin, and by forming fibrinopeptides (FDP) or D-dimer with their marked antithrombin effect—EACA would not have reversed these changes unless, as in this case, the patient's blood volume was continuously replenished. The sustained massive blood replacement not only restored the missing clotting factors but also kept the FDP concentration low despite the continuous and markedly enhanced plasminogen activator activity that was demonstrated in this patient.

Understandably, this new medication, which no one had ever heard of before, stirred up considerable interest and excitement on the surgical service. The news of the rapid response and spectacular cure reached the chief (Dr Owen Wangensteen), who stopped me in the hall a few days later to ask about the case. When I explained the problem to him, he seemed duly impressed.

All this took place before the existence of institutional review boards or research advisory committees, which later would come along to evaluate every research protocol to ensure its scientific merit and ethical correctness prior to approving or amending a new drug's use in patients. In fact, no one in those days felt any constraints to administer whatever became available, usually in a straightforward hit or miss approach, but in a way that would occasionally have a spectacular effect, as it did in this case.

Because we were under no obligation to obtain prior approval from the hospital or the patient to use this new medication, we began the next morning to study the changes in the patient's blood clotting parameters before, during, and after open-heart surgery to determine the effect of EACA on whatever changes did occur during and after surgery. (For performing these clinical trials the drug companies did not compensate researchers. This situation has changed. "Today two thirds of medical schools receive departmental income from drug companies while three fifths of the faculty received personal income leading at times to serious conflicts of interest." This has led to the disbursement of billions of dollars by the pharmaceutical industry according to M. Angell.)[3]

Ever since this event, this drug, or closely related antifibrinolytic agents, have been used during open-heart surgery to control hemorrhage after it was shown that they reduced bleeding and saved lives.[4] This case showed again that the intuitive approach and the chance clinical observation continued to play an important role in drug discovery. Quinidine's use for cardiac arrhythmias, phenylbutazone for arthritis, monoamino-oxidase inhibitors for depression, and sulphonureas for diabetes, all were recognized as useful drugs only accidentally or after patients received them for a different purpose.

Subsequently, we also observed that EACA is thrombogenic when given during a DIC.[5,6] Hence, its use should be curtailed after the neutralization of heparin[7,8] for this might well result in a postoperative cognitive dysfunction.[9]

REFERENCES

1. Alkjaersig N, Fletcher AP, Sherry S. Epsilon aminocaproic acid, an inhibitor of plasminogen activator. J Biol Chem 1959;234:832.
2. Gans H, Krivit W. Problems in hemostasis during open–heart surgery: III. Epsilon amino caproic acid an inhibitor of plasninogen activator activity. Ann Surg 1962;155: 268-76.
3. Angell M. Drug companies and doctors: a story of corruption. NY Rev Books 2009;56:8.
4. Sterns LP, Lillehei CW. Effect of epsilon aminocaproic acid upon blood loss following open heart surgery. An analysis of 340 patients. Can J Surg 1967;10:304-7.
5. Gans H. Use of epsilon amino caproic acid. Surg Gynecol Obstet 1965;120:576-7.
6. Gans H. Thrombogenic properties of epsilon amino caproic acid. Ann Surg 1966;163:175-8.
7. Castaneda AR, Gans H, Weber KC, Fox IJ. Heparin neutralization: experimental and clinical studies. Surgery 1967;62: 686-97.
8. Gans H, Castaneda AR. Problems in hemostasis during open heart surgery. VII. Changes in fibrinogen concentration during and after cardiopulmonary bypass with particular reference to the effect of heparin neutralization on fibrinogen. Ann Surg 1967;165:551-6.
9. Newman MF, Kirchner HL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 2001;344:395-402.