

DISCUSSION

DR. JOHN A. COLLINS (Stanford, California): As the authors have indicated, this material is now being looked at very hard, particularly in the dialysis solutions, where the amount that is given exceeds even the amount that is usually given in conjunction with Plasmanate. Indeed, there may be not only vasoactive but certain metabolic changes that are detrimental to the patient.

I would like to focus on the other part of the problem, that is, the part that deals with the PKA, or the bradykinin, or whatever else it is that might be in this solution that's causing trouble. I am not sure that the authors have established that there is not something else in addition to the acetate that has caused the difficulty.

The reason I say that is based on very soft data. A regulatory agency often has to work with soft data if there is a question of public safety and public good. I am not speaking officially now, but I have to point out that I was a member of the FDA panel which dealt with this question, and which withdrew certain lots of Plasmanate from the market. At the time (and even now in retrospect) the evidence in favor of something other than acetate in the solutions was, indeed, very compelling, although again I must acknowledge that it was soft.

There was clearly a marked cluster of deaths and serious reactions suddenly reported from various sources, associated with the use of Plasmanate. The FDA attempted to backcheck by doing a random sort of telephone interview of various institutions, including the ones that had reported difficulty, calling different people in that institution, and institutions that had not reported any difficulty. It turned up disturbing incidence of unreported serious reactions.

What was striking about this data is that it related only to certain lots of Plasmanate and not to all lots. That's where the question of cause really comes up, because all the lots of Plasmanate contained the same acetate content, but it was only certain peculiar lots that were associated with this apparently sudden increase in serious reactions.

One other line of evidence made this a fairly compelling argument. Those very lots of Plasmanate that turned out to be producing these serious reactions were lots that had been produced by a special method. The manufacturer, responding to the concerns about the levels of bradykinin in the material, changed the manufacturing process, and, indeed, got rid of bradykinin. In so doing, however, the manufacturer made the problem much worse than it had been.

It turns out, ironically, that bradykinin is probably a fairly benign material that does not cause much difficulty in the amount that was being infused into most patients. Whatever was done with the manufacturing process produced something else, which, based on the soft data, looked to be potentially extremely dangerous, and therefore the material was withdrawn from the market.

Now, the detective work currently points toward prekallikrein activator (PKA), but that by no means is a proven association. Trying to pinpoint what it is in this material that caused the difficulty has been a difficult job. I recommend the proceedings of a workshop held by the FDA with all the interested parties, including the manufacturer and investigators in the area. This workshop will be published soon.

Some of the things that came out of this workshop, however, are worth noting here. First of all, it is extremely difficult in biologic

models to reproduce whatever it was that was happening in patients. The models that were finally used were complex. Not just intact animals were used; the animals had to be modified in certain ways, and it worked only with certain species. In other words, whatever is in the material is difficult to identify with a bioassay.

Secondly, the investigative work that was done indicated that there may well be marked species differences in the response to this material, so I am not sure that being unable to show an effect in dogs carries over to prove that something does not exist for man.

Third, the clinical evidence indicated, as the authors have also indicated, that these reactions were seen mostly in critically ill patients, and, indeed, they tended to occur mostly in patients who were either on cardiopulmonary bypass or who were undergoing acute hemodialysis, but not chronic hemodialysis; they were undergoing dialysis for acute renal failure, with other complicating factors also present.

Whatever it is that was in this material that was causing the difficulty may, in fact, not even be manifest in patients who have intact defenses, but it may be manifest primarily in people who have already undergone a pretty extensive systemic inflammatory reaction.

With those concerns, I have one question for the authors. Where did you get the material that had the high PKA-level? Did this come from the manufacturer? Was this one of the lots that was implicated in reactions in humans? If it was, did you modify it in any way before you tested it?

DR. G. N. OLINGER (Closing discussion): Dr. Collins, your suggestion and that of the group that investigated the high PKA solutions that there may be something else going on in those particular solutions is of interest not only from the human data, but from our own animal data. In the dogs we studied with these solutions, we found a highly variable response.

Indeed, in two of the dogs there was a complete failure to recover vasoactive tone during the study, whereas in other animals there appeared to be very little response. We have been unable to determine what it is that makes one animal different from the other.

To answer your question regarding that material, it was provided to us by Cutter Laboratories, purely out of response to our questions. They were good enough to provide material to our specifications out of their experimental lots. I don't think the material that we obtained, high in PKA, was the same material that was used clinically because our solution was low in acetate, whereas most of the clinical material contained acetate in concentrations between 10 and 20 mEq/l and, as I have mentioned, as high as 60 mEq/l.

We agree that bradykinin is probably a fairly benign agent as long as it is infused on the right side of the circulation. However, when it is infused on the left side of the circulation, it is a potent vasodilator. It may act synergistically with whatever it is that causes vasodilation in response to acetate. The exact mechanism of acetate vasodilation, to my knowledge, is still not well known. It is purely a local effect on smooth muscle.

The acute renal failure patient is one that I think is particularly prone to the effects of Plasmanate, or PPF solutions, as well as to acetate. Patients critically ill with acute renal failure, particularly when limitation of cardiac output has contributed to renal failure, must be watched carefully to assure they do not get into further trouble during hemodialysis.