Editorial

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Use 'Em Together, I Tell You!

I have to admit that I'm wrong again. A battle I thought had been won some time ago hasn't really been won at all. A viewpoint opposite my own, a viewpoint I foolishly thought had been buried in the shifting sands of medical progress, continues to rear its ugly head with alarming frequency.

What am I raving about this time? Well, it's a topic of considerable importance. I'm talking about optimal management strategies for the treatment of type 2 diabetes mellitus. As we all know only too well, the rapidly expanding pandemic of type 2 diabetes threatens to become the Godzilla that ate the health care field, so widespread and so devastating are its many nefarious consequences.

Given that it's such a common and serious disease, you'd think we'd have some common understanding of how best to approach this disease. You'd think we'd all agree on some basic management principles of how best to tame this monster.

More specifically, and more to the point of my present diatribe, you'd think we'd agree on the basic principle of whether or not it makes sense to combine oral agents with insulin in the management of type 2 diabetes. You'd think everyone would pretty much be on the same wavelength here, but unfortunately, that's not true. Whereas I'm a firm advocate of combining oral agents with insulin in perpetuity, a sizable number of practitioners favor monotherapy with insulin for many of their patients. I beg to differ with their approach, and I feel strongly in my dissent.

A little bit of historical perspective may help here. When I was starting out as a very green, young endocrinologist in the late 1970s, it was standard practice to discontinue oral antidiabetic medications at the time that insulin therapy was initiated. The standard belief was that if patients couldn't get their blood sugar under control on oral agents alone, then the oral agents must have "failed" them somehow. Thus, these oral agents needed to be dispensed with in favor of the far more potent insulin, which could theoretically drive the blood sugar down just as far as you might choose to make it go. This approach never really made sense to me. How could it be that these agents had been more or less working for some time, only to be pitilessly dismissed as abject failures when the glucose level eventually started to creep up? Couldn't the fact that the patient was older, more obese, and less physically active have something to do with the supposed failure of these loyal antidiabetic worker bees? It seemed unreasonable and unjust to simply jettison them in favor of the supposedly sleek and more powerful insulin injections. But, then who was I to say? I was merely a wet-behind-the-ears novice doing mostly thyroid research; my opinions on the optimal management of diabetes were obviously amateurish and ill-informed.

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However, by the time I'd become a junior faculty member in the early 1980s, I occasionally began to come across articles in the literature that championed the idea of combining oral antidiabetic agents with insulin. So I started experimenting with combining the two, and I generally achieved reasonably good results. As the 1980s progressed, it became increasingly standard practice to combine them. I still believed that it made no sense to dump agents altogether that had been more or less getting the job done. (I'm obviously talking strictly about sulfonylureas here, because that was the only class we had in this country until the mid-1990s.) My philosophy was to give them a hand with some supplemental insulin, not the back of my hand for a supposed failure to control the diabetes.

I also had a couple of other concerns in mind, which I believe are still relevant today. For one, I was and am concerned that insulin is not entirely a benign agent, above and beyond its obvious potential to cause nasty hypoglycemic reactions. We've known for some time that insulin's central effects stimulate appetite centers in the hypothalamus, which can only lead to more mischief by causing weight gain, the last thing most patients with type 2 diabetes need. But, I also have a greater concern over the several different pathways that large quantities of insulin may find themselves traversing. One desirable pathway leads to glucose uptake in insulin-sensitive tissues such as fat, muscle, and liver. This is the "good" pathway that we are hoping insulin will follow when we flood the blood system with large exogenous

quantities of this potent hormone. There is also another potentially far less benign route for insulin known as the MAP-kinase pathway, which is essentially an anabolic route. Theoretically, activation of the MAP-kinase pathway can lead both to accelerated atherosclerosis and to malignancy. We already know that patients with diabetes are very much predisposed to both atherosclerosis and malignancy in the first place, so why overload the system with insulin and run the risk that a major portion of our drug will follow this pathway?

So for some years now, my approach has been to optimize oral therapy, particularly with the expanded range of oral agents now available, and then simply add whatever amount of insulin is needed to get to goal. By using less rather than more insulin, I hope to limit the amount of appetite stimulation and reduce any potential damage through stimulation of the MAP-kinase pathway. Don't let anyone tell you that medications such as sulfonylureas lose all their effectiveness over time. It's true that there is progressively less insulin to be squeezed out of the failing pancreas with time, but there's always some residual benefit to be derived from our old friends the sulfonylureas. I'd much rather squeeze out some endogenous insulin, with its physiologic delivery right into the portal vein, as opposed to flooding the system with insulin delivered through a decidedly unphysiologic route.

And, while I'm on this topic, a related concern of mine is the now-common practice of discontinuing oral agents in favor of using only insulin for patients with diabetes admitted to the hospital. This makes no sense either, apart from the possible (and largely overblown) concern of metformin accumulation if the patient were to become dehydrated. Why stop medications that have been working nicely because the patient with diabetes is now in the hospital? Hospital stays are typically quite brief these days, and the patient will need to be restarted on oral agents in just a few days. To the best of my knowledge, no randomized controlled trials support the discontinuation of oral agents on hospital admission, so I say don't do it. (Could this whole thing be some sort of conspiracy on the part of insulin manufacturers to get us to use more of their product if the patient doesn't get the oral agents restarted after discharge? I'm only half kidding, because the drug industry has aggressively pushed inpatient insulin titration regimens.)

So the bottom line in my mind is that one should almost always combine oral agents with insulin in patients with more severe type 2 diabetes, including hospitalized patients. A lesser dose of insulin makes more sense to me than a larger dose. Hopefully, it does to you, too. ●

Author disclosure

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