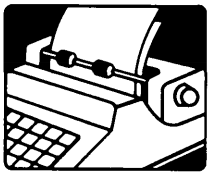
Editorial



A Plethora of Insulins

Elsewhere in this issue of DIABETES CARE appear two articles concerning insulin preparations. One, by Galloway, reviews insulin preparations currently available in the United States and articulates a viewpoint on the use of highly purified insulin, which recently became available on the American market.[1] The other, by Deckert, contrasts the two major intermediate-acting insulins, NPH and lente, in response to the oft-posed clinical question as to whether there is a basis for choice between them.[2] Although both are informative articles, it should be recognized that Galloway is associated with the Lilly Laboratory for Clinical Research and Deckert is associated with Steno Memorial Hospital, which is affiliated with Nordisk Insulinlaboratorium. Thus, by virtue of their connections with particular insulin manufacturers, there may be some bias to each of their viewpoints. In view of that, and the vigorous rivalry now taking place in the insulin market, an editorial comment seems to be in order.

The three major characteristics distinguishing insulin preparations are time course of action, species of origin, and degree of purity. These characteristics of insulins currently marketed in the United States are summarized in Table 1 in Galloway's article.[1] It should be noted that the two new entrants to the American market, Novo and Nordisk, have available for sale in this country only highly purified products. Lilly, too, markets highly purified single-species insulins, but the bulk of their sales is represented by their mixed-species (beef-pork) products of slightly lesser purity, a product they call "improved single peak" insulin.

Some confusion has developed with regard to insulin terminology. Partly, this is because Novo and Nordisk use different names to characterize some of their products than those familiar to Americans. For example, the familiar name in this country for rapid-acting unmodified insulin is "Regular," recognizable to many patients as "R." On the other hand, Novo's product is called "Actrapid" and designated "A," while Nordisk's product has been called both "Quick" and "Velosulin." In addition, Novo uses "Monotard" to designate its monospecies pork lente preparation, and "Lentard" to designate its mixed-species beef-pork lente preparation.

In addition to different product designations, terminology became complicated when the FDA permitted only the use of "highly purified" to designate those insulins with less than 10 ppm impurity, insulins that the medical literature over the past decade had termed "single component" or "monocomponent." Such highly purified insulins are now marketed in the United States by Lilly, Novo, and Nordisk. (Lilly's highly purified product is called "Iletin II." Novo and Nordisk market only "highly purified" insulins in this country.)

It should be noted, too, that Lilly has also further purified its standard product, which had come to be known in the literature as being of "single peak" purity, reducing the degree of impurity from 300–3000 ppm to less than 50 ppm. They termed this product "improved single peak" insulin, while labeling the bottle "New." Simultaneously, Lilly ceased production of monospecies "single peak" insulin, monospecies insulins now only being available in "highly purified" form.

Thus, in contrast to a year ago, we now have available insulins of higher purity. The monospecies pork insulins are of particular interest, because compared with other insulins, they have been found to be less immunogenic in human subjects.[3,4] Use of highly purified monospecies pork insulin has been found to be particularly beneficial in certain categories of patients: those with local or systemic insulin allergy,[5,6] immunologic insulin resistance,[7] or lipoatrophy at injection sites.[8,9] In addition, it seems reasonable to use highly purified pork insulin in individuals who are likely to be using insulin temporarily, since a history of interrupted insulin therapy is frequently reported in patients who present systemic insulin allergy or immunologic insulin resistance.[7] Circumstances in which temporary insulin use is likely include gestational-onset diabetes, insulin therapy in non-insulin-dependent patients during intercurrent infection or surgery, and insulin for patients receiving total parenteral nutrition.

Unresolved are the questions: (1) should patients previously treated with mixed-species (beef-pork) insulins be switched to highly purified monospecies pork insulins? and (2) should patients newly diagnosed as having diabetes be initiated on therapy with highly purified monospecies pork insulins?

Advocates of highly purified pork insulin for all patients argue that there is improved glycemic control, potential less-

ening of risk of complications, and that the cost difference (approximately double the price to the pharmacist for highly purified monospecies insulin than for mixed-species "improved single peak" insulin) is justified on the basis of an anticipated dose reduction on conversion to highly purified pork insulin. Unfortunately, there are no data to support any of these contentions. No long-term clinical trials exist to substantiate the first two claims. Regarding the dose reduction argument, varying degrees of dose reduction on conversion from "conventional" mixed-species beef-pork insulin to highly purified monospecies pork insulin have been reported in European studies.[10,11] However, the "conventional" mixed-species insulins used contained 10,000–80,000 ppm of impurities, so that the change in purity was radical. With lesser degrees of change in purity, i.e., from "single peak" beef-pork (300–3000 ppm impurities) to highly purified pork insulin (less than 10 ppm impurities), as shown in Galloway's Figure 2 elsewhere in this issue,[1] there was no predictable insulin dosage change. Yet, Schlichtkrull has contended that the dosage reductions noted in the European studies were dependent on the substitution of species, not on purity.[12] Suffice it to say that manufacturers are conducting further studies to help clarify this point. Thus, there are no data yet to justify switching patients previously treated with mixed-species insulins to highly purified pork insulin, in the absence of allergy, resistance, or lipoatrophy. Parenthetically, patients should be cautioned about switching brands of insulin because of considerable variation in purity, with some insulins marketed in this country (see Galloway, Table 1) still containing approximately 10,000 ppm impurities (although that is 99% pure, far different from the 92% purity of a decade ago).

The question of whether patients with newly diagnosed diabetes should be started on therapy with the least immunogenic insulin available is harder to answer. Certainly it seems logical that this would tend to lessen the induction of antibodies and would tend to decrease the risks of allergy, resistance, and lipoatrophy. Unfortunately, there are insufficient data to allow a firm conclusion that "highly purified" insulins with less than 10 ppm impurities are different in this regard from insulins with less than 50 ppm impurities ("improved single peak"). One would expect that they may be, but this could be due to species rather than purity differences. The question is complicated further by the contention that the use of "highly purified" insulin in newly diagnosed patients will leave them antibody-free at that point when human insulin (produced by recombinant DNA technology) becomes available. All other things being equal, including price, one would opt for the purist form, but price is approximately double. Thus the arguments are essentially those presented in the case of patients already receiving insulin, but with greater uncertainty, since there has been no previous exposure.

Finally, is there a basis for choice among the highly purified pork insulins? A basis for such a choice today is an economic one. The lowest priced product should win. However, economics are never simple. Local price variations among insulins are large. In the past, insulin often has been a "loss leader" to attract patients into pharmacies. With the introduction of "New" "improved single peak" insulin, many pharmacies have invoked full markups. Other pharmacists have encouraged patients to switch to highly purified pork insulin, resulting in an even greater cost increase. This is unfortunate for diabetic patients, who already are burdened with bourgeoning health care costs. It is hoped that professionals will give careful consideration to these issues before making recommendations to their patients.

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