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Human insulin

Problems with hypoglycaemia in a few patients

Last week the Committee on Safety of Medicines announced that with the British Diabetic Association it would be urgently investigating reports that some diabetics seemed to lose their normal warning symptoms of hypoglycaemia after their transfer from animal to human insulin.

At least three quarters of the 200 000 or so diabetic patients taking insulin in Britain are now injecting insulin of human sequence manufactured by either recombinant DNA technology or semisynthesis (enzymatic conversion from porcine insulin). In 1985-6 only about 6% of insulin sold in Britain was of the human type.[1] This massive changeover from animal insulins was encouraged by the withdrawal in 1986-7 of short acting and zinc suspension (lente type) porcine insulins by a leading manufacturer and their substitution by the equivalent human insulin formulations, by the change from producing bovine to producing human long acting insulin zinc suspension (ultralente), and by the increasing popularity of multiple injection regimens that use insulin "pens," which contain a cartridge of human insulin.[2] The promotion by most manufacturers of human insulin as a logical choice in the treatment of diabetes has also been an important factor; their commercial decision may be based on the not unreasonable desire to standardise production rather than on evidence of any important clinical advantage for human compared with porcine insulin treatment in most patients.

Most patients have been transferred to formulations of the human sequence insulin with little or no trouble, and most physicians have been happy for them to be managed in this way. In the past two years, however, as the switch to human insulin has accelerated, reports have begun to appear of adverse effects in a small number of patients with diabetes. In these cases the change from bovine or porcine to human insulin was associated with an increased frequency or a diminished awareness of hypoglycaemia, or both.

In 1987 Teuscher and Berger in Switzerland reported on three patients with insulin dependent diabetes who suffered severe hypoglycaemia without warning symptoms when switched from bovine or porcine insulin, or both, to human insulin.[3] When 176 patients who had made such a change were interviewed in a diabetic clinic 36% reported that their hypoglycaemic symptoms had changed from those associated with sympathoadrenal activation (sweating, tremor, palpitations, and so on) to those of neuroglycopenia (inability to concentrate, speech and visual disturbances, headache, and so on). This is an important observation because absent or reduced release of catecholamines in response to hypoglycaemia correlates with unawareness of hypoglycaemia,[4,5] a well established and extremely hazardous complication of insulin dependent diabetes.[6,7]

More recently Berger *et al* reported a double blind, randomised crossover trial of human and porcine insulin (short acting and isophane).[8] Though the number of hypoglycaemic episodes recorded by the patients and the self monitored glycaemic values at which the episodes occurred did not differ with the two regimens the initial symptoms seemed more often to be adrenergic with porcine insulin and "neuroglycopenic" with human insulin. This study can be criticised, however, for uncertainties about the selection of patients, the definition of hypoglycaemia, and the possible misclassification of symptoms as either adrenergic or neuroglycopenic; with these provisos the results do not unequivocally show a problem with human insulin.[9,10]

Letters from patients

Reports of unexpected and severe hypoglycaemia after transfer to human insulin have also, however, come from British sources.[11,12] The British Diabetic Association has received about 60 unsolicited letters from patients reporting hypoglycaemia with human insulin, sometimes with altered awareness, and these were about equally divided between those previously taking porcine insulin and those previously taking bovine insulin. The association sent out a questionnaire asking patients about their experiences on being changed to human insulin, and about half of those who had changed from animal insulin without other alterations in treatment thought that they were worse off as a result, mostly because of hypoglycaemia.[13]

There are good reasons why hypoglycaemia might increase after the initial transfer to human insulin treatment. Bovine insulin is known to be more immunogenic than porcine or human insulin,[14] from which it differs by three amino acids, and reductions in dosage of up to one fifth have been recommended by manufacturers for patients transferring from bovine to human insulin, particularly when the daily requirements with bovine insulin are high (>100 U/day or >1·5 U/kg/day). Unfortunately, one manufacturer initially suggested that most patients could be changed from bovine insulin on a dose for dose basis; this advice was clearly misleading—in one series a mean dosage reduction of about one quarter was required (range 6-51%), and, though the

larger reductions tended to be in patients previously taking large doses, a few patients taking small doses also needed large reductions.[15]

At the time of switching species the opportunity is also often taken to attempt to improve overall glycaemic control by introducing intensified injection regimens, increased self monitoring of blood glucose concentrations, renewed diabetes education, and so on. These measures also, however, increase the chance of low blood glucose values occurring. Strict control of blood glucose concentrations seems in itself to reduce the warning symptoms of hypoglycaemia, possibly by lowering the glycaemic threshold at which catecholamines are released.[16-18] Finally, patients who are unknowingly changed to a different insulin (sometimes by a pharmacist) or do not have a change of insulin species or injection regimen adequately explained by their doctor will clearly not be alerted to any altered insulin sensitivity or recognition of symptoms that might occur as a result of the factors mentioned above. In the British Diabetic Association's questionnaire such ill informed patients were specially likely to report difficulties.[13]

The crucial question is whether transfer from highly purified porcine insulin may lead in some patients to altered premonitory symptoms or an increased frequency of hypoglycaemia, or both, even when the transfer is done without additional alterations in treatment, with full explanation, and under medical supervision. Diabetic physicians had not expected this change in hypoglycaemia because of the close similarity in the pharmacology of the two insulins, and insulin manufacturers have not recommended any systematic reduction in dose.[1] There is as yet no convincing scientific evidence that treatment with porcine insulin should produce appreciably different metabolic effects from human insulin.[19] It has been said repeatedly that human insulin has the same biological potency as porcine insulin, both in vitro and when injected intravenously.[1] Human insulin is absorbed slightly more quickly from the site of subcutaneous injections,[1] so that initial prebreakfast blood glucose values are often a little higher during treatment with human than with porcine insulin,[20-22] probably because the intermediate acting human insulin is "running out." Many randomised controlled trials have shown, however, that there is no important difference in the number of hypoglycaemic episodes with the two treatments.[20-22] Counterregulatory hormone release is also the same after induction of hypoglycaemia by intravenous[23,24] or subcutaneous[19] administration of human or porcine insulin.

Few reports

The conclusion seems to be that if there is an increased risk of unexpected hypoglycaemia on transferring from porcine to human insulin it affects only a few patients. The manufacturer with the largest share of the insulin market in Britain (93% of sales being human insulin) has received only a small number of reports world wide of serious adverse events coded as hypoglycaemia or unawareness of hypoglycaemia—28 events in the past two and a half years, of which four were coded as unexpected (Novo Nordisk UK, personal communication). Another manufacturer has received a comparably small number of adverse reports about hypoglycaemia (Eli Lilly, personal communication). The Committee on Safety of Medicines has also received only a few notifications of adverse events with human insulin (personal communication). A recent survey in Britain showed that only about 6% of 302 randomly selected patients with insulin dependent diabetes reported diminished awareness of hypoglycaemia on switching from animal to human insulin.[25] The high proportion of 36% of patients reported by Teuscher and Berger may be an overestimate: it is unclear whether those with pre-existing unawareness during treatment with animal insulin were excluded from their survey.[3]

In many of the individual cases of hypoglycaemia with human insulin that may have been reported by doctors and patients the exact circumstances of the changeover have been difficult to discern—particularly the degree of glycaemic control before and after and often the number, type, and timing of the insulin injections. It could be argued that hypoglycaemia is fairly common in insulin dependent diabetes, whatever the treatment, and that on a few occasions patients could well attribute a chance increase in hypoglycaemia to some recent therapeutic manipulation. The introduction of highly purified (monocomponent) insulin and the change to U100 strength were both blamed for severe hypoglycaemia by some patients, though the extent of any such change is poorly documented.

Possible mechanisms

One clue to the mechanisms by which changes of treatment (such as the induction of strict glycaemic control) reduce the counterregulatory hormone response to hypoglycaemia has come from some observations by Gulan *et al.*[26] They looked at patients with diabetes in whom long term near normoglycaemia was obtained by either continuous subcutaneous insulin infusion or continuous intravenous insulin infusion. They found that in comparison with a period of conventional injection treatment the secretion of adrenaline and cortisol after hypoglycaemia was blunted after continuous subcutaneous insulin infusion but not after continuous intravenous insulin infusion. The mean blood glucose concentrations were the same with continuous subcutaneous insulin infusion and continuous intravenous insulin infusion (about 6·4 mmol/l), but glycaemic values were more variable and biochemical hypoglycaemia was more frequent during continuous subcutaneous insulin infusion. Possibly, therefore, it may be the frequency of hypoglycaemia rather than average control that reduces the release of counterregulatory hormones. Moreover, in normal people sustained mild hypoglycaemia for about one hour causes blood concentrations of adrenaline to increase, but awareness of hypoglycaemia is eventually lost, suggesting cerebral adaptation.[27] Possibly, in a small subset of patients with insulin dependent diabetes the absorption differences between human and porcine (and perhaps also bovine) insulin are especially noticeable, causing hypervariability in glycaemic control and either tolerance to frequent counterregulatory bursts or their diminution. Both the absorption of insulin and its effects on end organs are notoriously variable and unpredictable between and within subjects.[28,29] Such hypotheses need careful testing.

Where do we go from here? It seems both inevitable and correct that physicians and patients should use the time of a change in insulin species as an opportunity to review and optimise all aspects of each individual's treatment and thus attempt further to tighten glycaemic control. That this may lead to an increased number and alteration of warning symptoms of hypoglycaemia is a known risk. The effects of lower concentrations of antibody to insulin when changing from bovine insulin is an additional important hazard. None of the trials purporting to show differences in the perception and occurrence of hypoglycaemia during treatment with human versus porcine insulin are convincing, but neither can it be concluded that no such differences exist. There remains a case to answer.

Though the number of patients adversely affected is likely to be very small, the reasons for their susceptibility should be explored and means found to identify, predict, and minimise the problem. One of the most consistent complaints made

by patients in the correspondence on this topic sent to the British Diabetic Association is that doctors may refuse to acknowledge that a particular patient is having continued problems with human insulin despite adjustments in dose. In some cases changing back to the insulin species with which the diabetes was previously stabilised—either porcine or bovine—has been shown to restore warning symptoms of hypoglycaemia.[30] Doctors should, therefore, be aware of the risk of altered control, explain this risk to their patients (as well as the reasons for any changeover), and closely monitor the patient in the subsequent weeks. It is particularly necessary to warn patients of the danger of hypoglycaemia while driving and remind them of the need for checking blood glucose concentrations before the journey and at about two hourly intervals during long periods of driving. Doctors should take any adverse effects seriously and even be ready to change the patient back to animal insulin if necessary. Full ranges of both bovine and porcine insulins are still marketed in Britain. Finally, the British Licensing Authority has recently written to insulin manufacturers suggesting that the patient leaflets and the datasheets for human insulin should contain a specific warning that some patients have noted less pronounced symptoms of hypoglycaemia on transferring to human insulin from animal insulin. All insulin manufacturers have already made this change.

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Risk taking

A need for perspective

In midsummer the House of Commons Social Services Committee criticised the government for being slow in issuing information on food hygiene. Pregnant women could have been alerted to the hazards of listeria earlier, said the committee. These charges—and new proposals for improving food hygiene—are due to be debated when parliament reassembles. The committee was forthright in its criticism. But did it appreciate the problems in issuing public warnings? We are surrounded by risks, some of which are hard to ascertain, let alone set in perspective.

The doctor talking to an individual patient may find the question "What are the risks?"—for all its apparent simplicity—hard to answer. If he minimises the risks to spare a nervous patient anxiety then dissatisfaction and even legal action may ensue. Yet if every risk is spelt out important benefits of treatment may be lost. There may be something of a cry from the heart in David Kerr's comment: "I hope I shall never be expected to explain to my hypertensive patients, already reluctant to take their drugs regularly, that there is a remote risk of heart failure, asthma, jaundice, diabetes, impotence, nightmares, motor accidents, gout, depression, and writer's block."[1]

Difficult though it may be to inform and advise individual patients on complex issues, there are additional problems for those who have to issue general statements of advice to the public at large. There will always be people for whom general advice must be inappropriate. On any important matter, and perhaps particularly on health matters, any official statement is exposed at once to scrutiny by politicians and journalists, and both may wish to generate as much controversy and public noise as possible. The tone of the statement must be neither alarmist nor complacent, and it must be categorical, however uncertain the evidence underpinning it. It must also be made at the right time, neither a moment too soon nor a moment too late.

These difficulties are not always adequately recognised. The report of the social services committee on *Food Poisoning: Listeria and Listeriosis* asserted that "Too much information issued to the public on food safety and hygiene has come out in dribs and drabs. The Department of Health should have