

Diabetes Rate Up Among Inpatients in U.K. Study

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GLASGOW, SCOTLAND — The overall prevalence of diabetes among inpatients in Liverpool has increased significantly since 1990, according to a follow-up of one of the few studies of inpatient diabetes done during the 1980s and 1990s.

Researchers conducted a point-prevalence study to assess the extent of diabetes

among patients admitted to Aintree University Hospital in Liverpool for any reason in 1990. The study was repeated in 2003 to enable comparison of the changes in diabetes prevalence and hospital capacity.

“The strength of the studies is that we went round and examined all the case notes of everyone that was in hospital,” said Dr. Ian McFarlane, a consultant in the department of diabetes and endocrinology at the hospital, who presented the re-

sults at the Diabetes U.K. Annual Professional Conference. “But the drawback is that it is just a snapshot view.”

In 1990, the researchers identified 93 diabetes patients in the hospital. Their median age was 74 years and in 26% of cases, the primary admission was related to their diabetes. In 2003, there were more diabetic patients (126 versus 93), but fewer of the admissions—12.6%—were related to diabetes.

Overall, the prevalence of diabetes

among inpatients increased significantly from 7% in 1990 to 11.1% in 2003. The proportion of patients referred to the diabetes team also rose: from 10% in 1990 to 27.5% in 2003.

While prevalence of diabetes among inpatients seems to be increasing in line with national trends, the most worrisome figure for Dr. McFarlane was the small proportion of patients who were referred to the specialist team on admission. “Management is suboptimal in patients who are not referred to the diabetes team,” he said. “We considered management inappropriate in 20% of cases in 1990 and 27% in 2003.”

Examples of inappropriate care included high blood sugar being recorded but not followed up on and metformin being given to patients with renal failure. Only

48% of patients had records of diabetes complications present and only 24% had hemoglobin A_{1c} measurements “even though it should be done in everybody,” said Dr. McFarlane.

While the typical length of stay fell from

16 days in 1990 to 12 in 2003, Dr. McFarlane said this was related more to economic pressures than to better treatment. “The total hospital stay has fallen a bit with all the pressure to turn over beds, but people with diabetes still stay twice as long as those without,” he said.

To enable good management of inpatients with diabetes, Dr. McFarlane recommended the hospital use a multidisciplinary inpatient diabetes team that is on call 24 hours a day. He also suggested using a diabetes specialist nurse and ward-based diabetes “link” nurses to communicate with the specialist team, in addition to developing guidelines for diabetic emergencies and for procedures on wards.

One of the beneficial results of having done the 1990 study was to convince hospital managers that there was a substantial problem. “Having demonstrated the size of the problem, we managed to persuade the powers that be to fund an inpatient specialist nurse,” said Dr. McFarlane. “But if nurses turn over all the time, the skills that we help teach the staff nurse on the wards are blown around by all the vagaries of the nurses leaving,” he added.

The changes in diabetes demographics among inpatients have occurred against a background of substantial hospital changes in the United Kingdom. There are fewer hospital beds, increasing acute admissions, dramatic alterations to the out-of-hours care provided by general practitioners, and higher bed occupancy, said Dr. McFarlane. But it is the pressure to discharge early that causes inpatient care to fall apart. ■

Digoxin

There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (C_{max}, 18%) of digoxin with the coadministration of 100 mg sitagliptin for 10 days. These increases are not considered likely to be clinically meaningful. Digoxin, as a cationic drug, has the potential to compete with metformin for common renal tubular transport systems, thus affecting the serum concentrations of either digoxin, metformin or both. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or JANUMET is recommended.

Glyburide

In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide

A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32% without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

The Use of Metformin with Other Drugs

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving JANUMET the patient should be closely observed to maintain adequate glycemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B:

JANUMET

There are no adequate and well-controlled studies in pregnant women with JANUMET or its individual components; therefore, the safety of JANUMET in pregnant women is not known. JANUMET should be used during pregnancy only if clearly needed.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to JANUMET while pregnant. Health care providers are encouraged to report any prenatal exposure to JANUMET by calling the Pregnancy Registry at (800) 986-8999.

No animal studies have been conducted with the combined products in JANUMET to evaluate effects on reproduction. The following data are based on findings in studies performed with sitagliptin or metformin individually.

Sitagliptin

Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies with sitagliptin in pregnant women.

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30 and 20 times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Mothers

No studies in lactating animals have been conducted with the combined components of JANUMET. In studies performed with the individual components, both sitagliptin and metformin are secreted in the milk of lactating rats. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JANUMET is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of JANUMET in pediatric patients under 18 years have not been established.

Geriatric Use

JANUMET

Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, JANUMET should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function [see Warnings and Precautions].

Sitagliptin

Of the total number of subjects (N=3884) in Phase II and III clinical studies of sitagliptin, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin should only be used in patients with normal renal function. The initial and maintenance dosing of metformin should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function [see Contraindications; Warnings and Precautions].



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