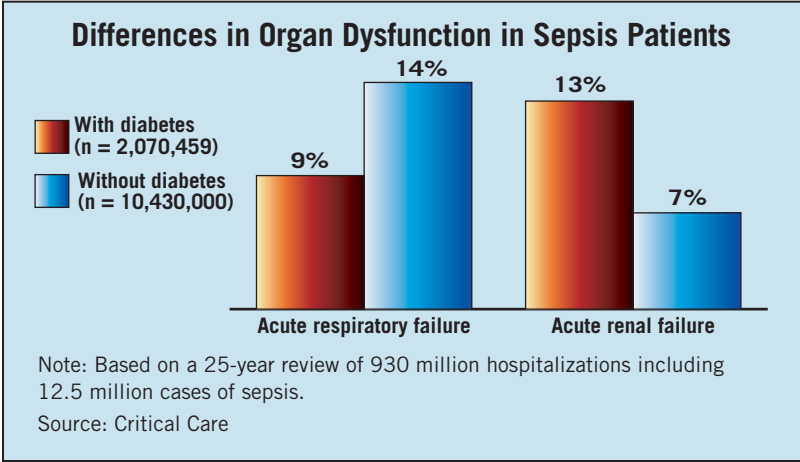




ADVERSE REACTIONS

Clinical Trials Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Sitagliptin and Metformin Co-administration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise. The most common (≥5% of patients) adverse reactions reported (regardless of investigator assessment of causality) in a 24-week placebo-controlled factorial study in which sitagliptin and metformin were co-administered to patients with type 2 diabetes inadequately controlled on diet and exercise were diarrhea (sitagliptin + metformin [N=372], 7.5%; placebo [N=176], 4.0%), upper respiratory tract infection (6.2%, 5.1%), and headache (5.9%, 2.8%).

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone. In a 24-week placebo-controlled trial of sitagliptin 100 mg administered once daily added to a twice daily metformin regimen, there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo. Discontinuation of therapy due to clinical adverse reactions was similar to the placebo treatment group (sitagliptin and metformin, 1.9%; placebo and metformin, 2.5%).

Hypoglycemia. Adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required. The overall incidence of pre-specified adverse reactions of hypoglycemia in patients with type 2 diabetes inadequately controlled on diet and exercise was 0.6% in patients given placebo, 0.6% in patients given sitagliptin alone, 0.8% in patients given metformin alone, and 1.6% in patients given sitagliptin in combination with metformin. In patients with type 2 diabetes inadequately controlled on metformin alone, the overall incidence of adverse reactions of hypoglycemia was 1.3% in patients given add-on sitagliptin and 2.1% in patients given add-on placebo.

Gastrointestinal Adverse Reactions. In patients treated with sitagliptin and metformin vs patients treated with metformin alone, incidences of pre-selected gastrointestinal adverse reactions were diarrhea (sitagliptin + metformin [N=464], 2.4%; placebo + metformin [N=237], 2.5%), nausea (1.3%, 0.8%), vomiting (1.1%, 0.8%), and abdominal pain (2.2%, 3.8%).

Sitagliptin in Combination with Metformin and Glimepiride. In a 24-week placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin and glimepiride (sitagliptin, N=116; placebo, N=113), the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: hypoglycemia (sitagliptin, 16.4%; placebo, 0.9%) and headache (6.9%, 2.7%).

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed with the combination of sitagliptin and metformin.

The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo was nasopharyngitis.

The most common (>5%) established adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

Laboratory Tests.

Sitagliptin. The incidence of laboratory adverse reactions was similar in patients treated with sitagliptin and metformin (7.6%) compared to patients treated with placebo and metformin (8.7%). In most but not all studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs placebo; mean baseline WBC approximately 6600 cells/microL) was observed due to a small increase in neutrophils. This change in laboratory parameters is not considered to be clinically relevant.

Metformin hydrochloride. In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B₁₂ levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B₁₂ supplementation [see Warnings and Precautions].

Postmarketing Experience. The following additional adverse reactions have been identified during postapproval use of JANUMET or sitagliptin, one of the components of JANUMET. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions include anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome [see Warnings and Precautions]; upper respiratory tract infection; hepatic enzyme elevations; pancreatitis.

DRUG INTERACTIONS

Cationic Drugs. Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of JANUMET and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

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 co-administration 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, co-administration 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.

Respiratory Failure Less Likely In Sepsis Patients With Diabetes

BY HEIDI SPLETE

Sepsis patients with diabetes are significantly less likely to experience acute respiratory failure than are patients without diabetes, according to data from a review of 930 million hospitalizations over 25 years.

Previous studies have shown that sepsis is common in people with diabetes, and that those pa-

tients are less likely to develop acute lung injuries as a result of sepsis. But those studies did not compare organ dysfunction in sepsis patients with and without diabetes.

Dr. Annette Esper of Emory University in Atlanta and her colleagues reviewed National Hospital Discharge Survey data from 1979-2003. The researchers used ICD-9 codes to identify cases of sepsis and the sources of the infections. The researchers identified 12.5 million cases of sepsis, and 17% of the patients had diabetes. Among the population of patients with diabetes and sepsis, 57% were women, and 64% were white. The average patient age was 68 years.

Overall, patients with diabetes and sepsis were significantly more likely to develop acute renal failure than were patients without diabetes, but were significantly less likely to develop acute respiratory failure (see chart) [Crit. Care 2009 Feb. 12 [doi: 10.1186/cc7717]].

No other significant differences appeared in the occurrence of other organ dysfunctions, or in the average total number of organ dysfunctions in the two groups. However, the difference in acute respiratory failure persisted regardless of the source of infection. Among patients with a respiratory source of sepsis, those with diabetes were significantly less likely to develop acute respiratory failure than were those without diabetes (16% vs. 23%). The difference in acute respiratory failure rates was also significant for patients with and without diabetes (6% vs. 10%) who had nonpulmonary sources of infection.

The overall fatality rate for sepsis patients with diabetes was significantly lower than for those without diabetes (19% vs. 21%), but fatality rates between patients with and without diabetes who developed acute respiratory failure were not significantly different (52% vs. 48%).

The reasons for the distinction in respiratory failure rates between patients with and without diabetes remain uncertain. Theories include the potential blunted inflammatory response to organ dysfunction in people with diabetes, the investigators said, and the possibility that diabetes patients may be hospitalized for sepsis sooner because they may be more alert to signs of infection. Diabetes medications may play a role, too.

“Pharmacological aspects of [diabetes] may also influence the development of organ dysfunction, because many medications administered to patients with [diabetes], including insulin and thiazolidinediones, are known to have anti-inflammatory effects in addition to lowering blood glucose,” the researchers noted.

But more research is needed to show the effects of diabetes medications and other factors on respiratory problems in sepsis patients in order to develop more effective treatments, they added.

The researchers had no financial conflicts to disclose.

Furosemide. A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. 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 co-administered chronically.

Nifedipine. A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration 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 co-administered 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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