

Sulfonylureas Tied to Mortality in MI Survivors

BY BRUCE JANCIN

BARCELONA — Four widely prescribed oral sulfonylurea drugs are associated with significantly increased risk of all-cause mortality compared with metformin in type 2 diabetic patients having a history of MI, according to a comprehensive Danish national cohort study.

The study included all Danish adults with a prior MI who started on oral glu-

cose-lowering monotherapy during 1997-2006. The conclusion: Glimepiride, glyburide, glipizide, and tolbutamide were associated with 33%-43% higher mortality risk than was metformin, Dr. Tina Ken Schramm said at the annual congress of the European Society of Cardiology.

In contrast, single-agent gliclazide and repaglinide had all-cause mortality risks similar to metformin.

"The clinical implication of this is that

metformin, gliclazide, and repaglinide appear superior to other single-drug treatments received. We believe that metformin in general should be part of the treatment of type 2 diabetes to reduce mortality, but gliclazide and repaglinide may be good alternatives," said Dr. Schramm of the Heart Center at Copenhagen University National Hospital.

Metformin deserves the nod as the first-line agent on the basis of the results

of the landmark United Kingdom Prospective Diabetes Study, which convincingly established the drug as the safest glucose-lowering agent available.

Out of the total Danish population of roughly 4.1 million, 107,870 type 2 diabetic individuals initiated monotherapy with a glucose-lowering agent during the 9-year study period. Among them were 9,135 with a prior MI, who formed the population for this study.

Glimepiride was the most widely prescribed of the glucose-lowering medications in Denmark, being used by 43% of subjects. Next came metformin (32%), glyburide (13%), glipizide and gliclazide (7% each), tolbutamide (6%), and repaglinide (2%). Acarbose was prescribed

CYP 450 Interactions: *In vitro* metabolism studies have indicated that CYP450 mediated drug interactions between valsartan and coadministered drugs are unlikely because of low extent of metabolism [see *Pharmacokinetics - Valsartan (12.3) in the full prescribing information*].

Transporters: The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Coadministration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see *Warnings and Precautions (5.1)*]. Valtorna contains both aliskiren (a direct renin inhibitor) and valsartan (an angiotensin II receptor blocker). When administered during the second or third trimester of pregnancy, drugs that act directly on the renin-angiotensin-aldosterone system can cause fetal and neonatal morbidity and death. Valtorna can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus.

Angiotensin II receptor antagonists, like valsartan, and angiotensin-converting enzyme (ACE) inhibitors exert similar effects on the renin-angiotensin-aldosterone system. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios was also reported, presumably from decreased fetal renal function. In this setting, oligohydramnios was associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus were also reported, although it is not clear whether these occurrences were due to exposure to the drug. In addition, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin-angiotensin-aldosterone system, has been associated with a potential risk of birth defects in retrospective data.

When pregnancy occurs in a patient using Valtorna, discontinue Valtorna treatment as soon as possible. Inform the patient about potential risks to the fetus based on the time of gestational exposure to Valtorna (first trimester only or later). If exposure occurs beyond the first trimester, perform an ultrasound examination.

In rare cases when another antihypertensive agent cannot be used to treat the pregnant patient, perform serial ultrasound examinations to assess the intraamniotic environment. Routine fetal testing with non-stress tests, biophysical profiles, and/or contraction stress tests may be appropriate based on gestational age and standards of care in the community. If oligohydramnios occurs in these situations, individualized decisions about continuing or discontinuing Valtorna treatment and about pregnancy management should be made by the patient, her physician, and experts in the management of high risk pregnancy. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Closely observe infants with histories of *in utero* exposure to Valtorna for hypotension, oliguria, and hyperkalemia. If oliguria occurs, these infants may require blood pressure and renal perfusion support. Exchange transfusion or dialysis may be required to reverse hypotension or support decreased renal function.

No reproductive toxicity studies have been conducted with the combination of aliskiren and valsartan. However, these studies have been conducted for aliskiren as well as valsartan alone [see *Nonclinical Toxicology (13) in the full prescribing information*].

8.3 Nursing Mothers

It is not known whether aliskiren is excreted in human milk, but aliskiren was secreted in the milk of lactating rats. It is not known whether valsartan is excreted in human milk. Valsartan was excreted into the milk of lactating rats; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of Valtorna in pediatric patients have not been established.

8.5 Geriatric Use

In the short-term controlled clinical trials of Valtorna, 99 (15.9%) patients treated with Valtorna were ≥ 65 years and 14 (2.2%) were ≥ 75 years.

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

Aliskiren

Limited data are available related to overdose in humans. The most likely manifestation of overdose would be hypotension. If symptomatic hypotension occurs, provide supportive treatment.

Valsartan

Limited data are available related to overdose in humans. The most likely effect of overdose with valsartan would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension occurs, provide supportive treatment.

Valsartan is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for the salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 31 times, respectively, the maximum recommended human dose on a mg/m² basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

16 STORAGE

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in original container. [See USP Controlled Room Temperature.]

Protect from moisture.

Dispense in tight container (USP).

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Glimepiride, glyburide, glipizide, and tolbutamide were associated with higher mortality than metformin.

DR. SCHRAMM

as monotherapy in only 44 patients nationwide—far too small a number to allow meaningful results. Similarly, the thiazolidinediones, which in Denmark are not recommended therapy in this clinical setting, were used too seldom to draw any conclusions, explained Dr. Schramm, who reported having no financial conflicts of interest regarding the study.

Metformin served as the comparator in determining all-cause mortality risks for the other oral glucose-lowering agents in a multivariate analysis adjusted for age, gender, years of diabetes, cardiovascular medications, and socioeconomic status.

Audience members asked if confounding was a potential issue in the study—that is, perhaps patients on drugs other than metformin were sicker, or had previously been on metformin but proved intolerant or unresponsive to it. Dr. Schramm replied that it's unlikely, since when she performed a subanalysis restricted to those patients starting their first-ever glucose-lowering agent the results were unchanged.

She undertook the study because most prior trials oral glucose-lowering medications did not look beyond glucose-lowering efficacy in terms of outcomes. ■

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