BY MILES J. ZAREMSKI, J.D.

LAW & MEDICINE

Adverse Event Confidentiality

Imagine being a physician who has been involved in an adverse event—one that, through no real fault of your own, caused death or serious injury to a patient. Should your future patients have a right to know of your involvement?

Florida physicians are dealing with this issue in the wake of a recent decision by the Florida Supreme Court earlier this year, in *Florida Hospital Waterman, Inc. etc., v. Teresa M. Buster, etc., et al.* (No. SC06-912). In November 2004, Florida voters passed a constitutional amendment titled "Patients' Right to Know About Adverse Medical Incidents." The amendment let patients obtain "any records made or received in the course of business by a health care facility or provider relating to any adverse medical incident"—as long as the identity of the patients involved in the incidents wasn't revealed, and other privacy restrictions were adhered to. This included incidents that had to be reported to a government agency, or those that were reported to health care facility review committees. The amendment was to become effective immediately.

About 6 months later, in June 2005, the Florida legislature tried to clarify the amendment legislatively, stating that existing restrictions on use of records in court cases stay in place and that "discovering such documents does not mean that any of them can be introduced into evidence in a lawsuit … and [they] may not be used for any purpose, including impeachment, in any civil or administrative action against a health care facility or health care provider."

Because of the legislature's action, two lower courts in Florida were asked to decide whether the amendment passed by the voters applied retroactively to records that existed before the amendment was passed. One court held that the amendment was retroactive; the other did not. In a 4-3 decision (with a sharply worded dissent), the Florida Supreme Court found that the amendment was indeed retroactive. The court also found that several subsections of new law were in conflict with the amendment passed by the voters, and were thus unconstitutional.

The majority eviscerates what has become the linchpin for a health care facility's ability to ensure quality of care: its peer review function.

The Florida high court noted that access to peer review information is not to be limited to only those who are themselves patients since that restriction is not contained within the amendment.

But more importantly, the court also said that because part of the new law allows current laws restricting access to adverse incidents to remain in place, the new law is in conflict with the amendment passed by the voters and therefore "cannot stand."

The dissenting justices argued that the amendment should not be applied retroactively. They noted that hospitals are required to perform peer review as part of medical quality assurance, and that the hospitals should be able to keep peer review records from being used in legal cases. Now that the majority has found the amendment to be retroactive, the dissenters pointed out, that allows for the discovery of records previously kept confidential, a consequence that is "legally unsupportable" and "fundamentally unfair."

The Florida Supreme Court goofed. In its fervor to address the issue of retroactivity, it created more of a problem than it should have. The majority eviscerates what has become the linchpin for a health care facility's ability to ensure quality of care: its peer review function.

For example, let's take a situation in which a hospital's peer review committee obtains documents relating to an adverse medical incident. From those documents, the peer review committee makes a decision about the care rendered by a particular doctor.

Before the *Florida Hospital Waterman*

Continued on following page

Tekturna® (aliskiren) Tablets
150 mg and 300 mg
Rx only
BRIEF SUMMARY: Please see package insert for full prescribing information.

USE IN PREGNANCY: When used in pregnancy drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Tekturna should be discontinued as soon as possible. See **WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

INDICATIONS AND USAGE
Tekturna® (aliskiren) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. Use with maximal doses of ACE inhibitors has not been adequately studied.

WARNINGS
Fetal/Neonatal Morbidity and Mortality
Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, Tekturna® (aliskiren) should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been 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 system, has been associated with a potential risk of birth defects in retrospective data. Healthcare professionals that prescribe drugs acting directly on the renin-angiotensin system should counsel women of childbearing potential about the potential risks of these agents during pregnancy.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, Tekturna should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in-utero exposure to a renin inhibitor should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

There is no clinical experience with the use of Tekturna in pregnant women. Reproductive toxicity studies of aliskiren hemifumarate did not reveal any evidence of teratogenicity at oral doses up to 600 mg aliskiren/kg/day (20 times the maximum recommended human dose (MRHD) of 300 mg/day on a mg/m² basis) in pregnant rats or up to 100 mg aliskiren/kg/day (seven times the MRHD on a mg/m² basis) in pregnant rabbits. Fetal birth weight was adversely affected in rabbits at 50 mg/kg/day (3.2 times the MRHD on a mg/m² basis). Aliskiren was present in placenta, amniotic fluid and fetuses of pregnant rabbits.

Head and Neck Angioedema
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with aliskiren. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in Black than in non-Black patients, but whether angioedema rates are higher in Blacks with aliskiren is not known. Tekturna should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Experience with ACE inhibitors indicates that even in those instances where only swelling of the tongue is seen initially, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Very rarely, fatalities have been reported in patients with angioedema associated with laryngeal edema or tongue edema with ACE inhibitors. Patients with involvement of the tongue, glottis or larynx are more likely to experience airway obstruction, especially those with a history of airway surgery. Where there is involvement of the tongue, glottis or larynx, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and measures necessary to ensure a patent airway should be promptly provided (see ADVERSE REACTIONS).

Hypotension
An excessive fall in blood pressure was rarely seen (0.1%) in patients with uncomplicated hypertension treated with Tekturna alone. Hypotension was also infrequent during combination therapy with other antihypertensive agents (<1%). In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those receiving high doses of diuretics), symptomatic hypotension could occur after initiation of treatment with Tekturna. This condition should be corrected prior to administration of Tekturna, or the treatment should start under close medical supervision.

If an excessive fall in blood pressure occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline (see DOSAGE AND ADMINISTRATION in the full prescribing information). A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS
General
Impaired Renal Function
Patients with greater than moderate renal dysfunction (creatinine 1.7 mg/dL for women and 2.0 mg/dL for men and/or estimated GFR <30 mL/min), a history of dialysis, nephrotic syndrome, or renovascular hypertension were excluded from clinical trials of Tekturna® (aliskiren) in hypertension. Caution should be exercised in these patients because of the paucity of safety information with Tekturna in these patients and the potential for other drugs acting on the renin-angiotensin system to increase serum creatinine and blood urea nitrogen.

Hyperkalemia
Increases in serum potassium >5.5 meq/L were infrequent with Tekturna alone (0.9% compared to 0.6% with placebo). However, when used in combination with an ACE inhibitor in a diabetic population, increases in serum potassium were more frequent (5.5%). Routine monitoring of electrolytes and renal function is indicated in this population. Concomitant use of Tekturna with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that increase potassium levels may lead to increases in serum potassium. If concomitant use is considered necessary, caution should be exercised.

Renal Artery Stenosis
No data are available on the use of Tekturna in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Information for Patients
Pregnancy
Female patients of childbearing age should be told about the consequences of exposure to drugs that act on the renin-angiotensin system. Discuss other treatment options with female patients planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema
Angioedema, including laryngeal edema, may occur at any time during treatment with Tekturna. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Drug Interactions
Patients should report any medications they take with aliskiren.

Furosemide
When aliskiren was given with furosemide, the blood concentrations of furosemide were reduced significantly. Patients receiving furosemide could find its effect diminished after starting aliskiren.

Cyclosporine
When aliskiren was given with cyclosporine, the blood concentrations of aliskiren were significantly increased. Concomitant use of aliskiren with cyclosporine is not recommended.

Carcinogenesis/Mutagenesis/Impairment of Fertility
Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic (rasH2) mouse study with aliskiren hemifumarate at oral doses of up to 1500 mg aliskiren/kg/day. Although there were no statistically significant increases in tumor incidence associated with exposure to aliskiren, mucosal epithelial hyperplasia (with or without erosion/ulceration) was observed in the lower gastrointestinal tract at doses of 750 or more mg/kg/day in both species, with a colonic adenoma identified in one rat and a cecal adenocarcinoma identified in another, rare tumors in the strain of rat studied. On a systemic exposure ($AUC_{0\text{-}24hr}$) basis, 1500 mg/kg/day in the rat is about 4 times, and is in the mouse about 1.5 times, the maximum recommended human dose (300 mg aliskiren/day). Mucosal hyperplasia in the cecum or colon of rats was also observed at oral doses of 250 mg/kg/day (the lowest tested dose) as well as at higher doses in 4- and 13-week studies.

Aliskiren hemifumarate was devoid of genotoxic potential in the Ames reverse mutation assay with S. typhimurium and E. coli, the in vitro Chinese hamster ovary cell chromosomal aberration assay, the in vitro Chinese hamster V79 cell gene mutation test and the in vivo mouse bone marrow micronucleus assay.

Fertility of male and female rats was unaffected at doses of up to 250 mg aliskiren/kg/day (8 times the maximum recommended human dose of 300 mg Tekturna/60 kg on a mg/m² basis).

Pregnancy
Pregnancy Categories C (first trimester) and D (second and third trimesters) (see WARNINGS, Fetal/Neonatal Morbidity and Mortality).

Nursing Mothers
It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats. 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.

Pediatric Use
Safety and effectiveness of aliskiren in pediatric patients have not been established.

Geriatric Use
Of the total number of patients receiving aliskiren in clinical studies, 1,275 (19%) were 65 years or older and 231 (3.4%) were 75 years or older. Blood pressure responses and adverse effects were generally similar to those in younger patients.

ADVERSE REACTIONS
Tekturna® (aliskiren) has been evaluated for safety in more than 6,460 patients, including over 1,740 treated for longer than 6 months, and more than 1,250 for longer than 1 year. In placebo-controlled clinical trials, discontinuation of therapy due to a clinical adverse event, including uncontrolled hypertension occurred in 2.2% of patients treated with Tekturna, vs. 3.5% of patients given placebo.

Two cases of angioedema with respiratory symptoms were reported with aliskiren use in the clinical studies. Two other cases of periorbital edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06%.

In addition, 26 other cases of edema involving the face, hands, or whole body were reported with aliskiren use, including 4 leading to discontinuation.

In the placebo controlled studies, however, the incidence of edema involving the face, hands or whole body was 0.4% with aliskiren compared with 0.5% with placebo. In a long term active control study with aliskiren and HCTZ arms, the incidence of edema involving the face, hand or whole body was 0.4% in both treatment arms.

Aliskiren produces dose-related gastrointestinal (GI) adverse effects. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age ≥65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups at 150 mg comparable to those seen at 300 mg for men or younger patients (all rates about 2.0%-2.3%). Other GI symptoms included abdominal pain, dyspepsia, and gastroesophageal reflux, although increased rates for abdominal pain and dyspepsia were distinguished from placebo only at 600 mg daily. Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation.

Aliskiren was associated with a slight increase in cough in the placebo-controlled studies (1.1% for any aliskiren use vs. 0.6% for placebo). In active-controlled trials with ACE inhibitor (ramipril, lisinopril) arms, the rates of cough for the aliskiren arms were about one-third to one-half the rates in the ACE inhibitor arms.

Other adverse effects with increased rates for aliskiren compared to placebo included rash (1% vs. 0.3%), elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%).

Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients treated with aliskiren in the clinical trials. One of these patients did have predisposing causes for seizures and had a negative electroencephalogram (EEG) and cerebral imaging following the seizures (for the other patient EEG and imaging results were not reported). Aliskiren was discontinued and there was no rechallenge.

The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with aliskiren, but also occurred at about the same or greater incidence in patients receiving placebo: headache, nasopharyngitis, dizziness, fatigue, upper respiratory tract infection, back pain, and cough.

Clinical Laboratory Findings
In controlled clinical trials, clinically relevant changes in standard laboratory parameters were rarely associated with the administration of Tekturna. In multiple-dose studies in hypertensive patients Tekturna had no clinically important effects on total cholesterol, HDL, fasting triglycerides, fasting glucose, or uric acid.

Blood Urea Nitrogen, Creatinine
Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 7% of patients with essential hypertension treated with Tekturna alone vs. 6% on placebo.

Hemoglobin and Hematocrit
Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.08 g/dL and 0.16 volume percent, respectively, for all aliskiren monotherapy) were observed. The decreases were dose-related and were 0.24 g/dL and 0.79 volume percent for 600 mg daily. This effect is also seen with other agents acting on the renin-angiotensin system, such as angiotensin inhibitors and angiotensin receptor blockers, and may be mediated by reduction of angiotensin II which stimulates erythropoietin production via the AT1 receptor. These decreases led to slight increases in rates of anemia with aliskiren compared to placebo were observed (0.1% for any aliskiren use, 0.3% for aliskiren 600 mg daily, vs. 0% for placebo). No patients discontinued therapy due to anemia.

Serum Potassium
Increases in serum potassium >5.5 meq/L were infrequent in patients with essential hypertension treated with Tekturna alone (0.9% compared to 0.6% with placebo). However, when used in combination with an angiotensin-converting enzyme inhibitor (ACEI) in a diabetic population increases in serum potassium were more frequent (5.5%) and routine monitoring of electrolytes and renal function is indicated in this population.

Serum Uric Acid
Aliskiren monotherapy produced small median increases in serum uric acid levels (about 6 µmol/L) while HCTZ produced larger increases (about 30 µmol/L). The combination of aliskiren with HCTZ appears to be additive (about a 40 µmol/L increase). The increases in uric acid appear to lead to slight increases in uric acid-related AEs: elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%).

Creatine Kinase
Increases in creatine kinase of >300% were recorded in about 1% of aliskiren monotherapy patients vs. 0.5% of placebo patients. Five cases of creatine kinase rises, three leading to discontinuation and one diagnosed as subclinical rhabdomyolysis and another as myositis, were reported as adverse events with aliskiren use in the clinical trials. No cases were associated with renal dysfunction.

OVERDOSAGE
Limited data are available related to overdosage in humans. The most likely manifestation of overdosage would be hypotension. If symptomatic hypotension should occur, supportive treatment should be initiated.

Storage
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Protect from moisture. Dispense in tight container (USP).

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case came down, there was an expectation that documents considered by a peer review committee would be privileged from discovery and not admissible in a legal proceeding. With *Florida Hospital Waterman*, no longer would such documents be cloaked with the protections against discovery provided in Florida. This would be inconsistent with protections against discovery provided in most—if not all—states having peer review statutes.

And, again, according to *Florida Hospital Waterman*, the right to see such evidence can pertain to documents that existed as of the date the Florida voters passed the constitutional amendment. How far back can the documents go? The court never says.

Another problem is that, for example, an accrediting organization such as the Joint Commission—which credentials a considerable portion of our nation's hospitals and other health care facilities—may find some difficulty with the *Florida Hospital Waterman*'s majority's decision. One area the Joint Commission looks at in its accreditation process are "sentinel events"—those involving deaths or serious injuries. What if a sentinel event is intertwined with an adverse medical incident? All such information would be usable in legal cases under *Florida Hospital Waterman*, which may make hospital administrators uncomfortable if the commission asks them to produce sentinel event information during an accreditation or reaccreditation process.

Then there is the privacy issue. If privacy laws such as the Health Insurance Portability and Accountability Act (HIPAA) are to be respected, what good is producing an adverse medical incident report that is required by HIPAA but not including identifying information about the patient? HIPAA would thus destroy much of the good intended by the amendment passed by the voters. Moreover, since the amendment doesn't specify exactly who is entitled to such records, then anyone can request such information, regardless of applicable state or federal privacy laws.

Last, but certainly not least, are evidence laws relating to adverse medical incident records. The Florida high court blundered when it stated that a restriction on admitting such records in court cannot stand. Surely the decision on whether the constitutional amendment was retroactive was never intended to circumvent Florida's laws regulating the admissibility of evidence. Yet this is a conundrum that the court majority has now created.

The law is never precise, and many times its development can raise more issues than it solves. That is what has happened here. What the Florida Supreme Court has done needs fixing—by the court somehow amending its decision, or by the Florida legislature harmonizing state law with the constitutional amendment passed by Florida's voters, or by having Florida voters amend the state constitution in some fashion. Only then can physicians in Florida and elsewhere be assured that the confidential work of peer review committees and accreditation organizations will remain confidential. ■

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Resource on Health Care Innovations

The Agency for Healthcare Research and Quality has launched a new Web resource called the Health Care Innovations Exchange to share examples of both successful and unsuccessful attempts at innovation in health care.

After starting out with 100 examples, it will be updated every 2 weeks. Visit www.innovations.ahrq.gov.

INDEX OF ADVERTISERS

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