

Donor Management Boosted Heart Procurement

BY NEIL OSTERWEIL

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BOSTON – It seems counterintuitive, but when management times of potential heart and lung donors stretched beyond 20 hours, successful organ procurement rates at one center actually went up rather than down, investigators reported.

Among 42 donors managed for 20 hours or less, only six lungs (7% of possible total) and five hearts (12%) could be procured. In contrast, among 58 donors managed for more than 20 hours, 40 lungs (34%) and 26 hearts (45%) could be procured.

The surprising findings, from a prospective analysis of 100 consecutive organ donors, occurred despite the fact that there were no significant differences in at-

tainment of preprocurement donor-management goals, said Dr. A. Britton Christmas of the surgery department at the Carolinas Medical Center, Charlotte, N.C.

A total of 133 organs, mean 3.2/donor, were obtained from donors managed 20 hours or less, and 243, mean 4.2/donor, from those managed for more than 20 hours (*P* less than .01). There was a mean of 2.6 organs transplanted for each donor managed 20 hours or less, and 3.7 for

each managed for more than 20 hours (*P* less than .01).

“The general consensus is that early procurement removes the transplant organ from a hostile environment, but we believe that this study provides evidence to the contrary. Perhaps the reward really is worth the wait,” Dr. Christmas said.

Their original hypothesis was that shorter management times would yield higher organ procurement and transplant rates in general and heart and lung transplants in particular.

The investigators collaborated with the organ procurement organization LifeShare of the Carolinas, which covers

Pharmacodynamic interactions can be expected with beta-blockers; calcium antagonists and digoxin [see *Drug Interactions (7.1)*].

In clinical trials, patients treated with dronedarone received concomitant medications including beta-blockers, digoxin, calcium antagonists (including those with heart rate-lowering effects), statins and oral anticoagulants.

7.1 Pharmacodynamic Interactions

Drugs prolonging the QT interval (inducing Torsade de Pointes)

Co-administration of drugs prolonging the QT interval (such as certain phenothiazines, tricyclic antidepressants, certain macrolide antibiotics, and Class I and III antiarrhythmics) is contraindicated because of the potential risk of Torsade de Pointes-type ventricular tachycardia [see *Contraindications (4)*].

Digoxin

Digoxin can potentiate the electrophysiologic effects of dronedarone (such as decreased AV-node conduction). In clinical trials, increased levels of digoxin were observed when dronedarone was co-administered with digoxin. Gastrointestinal disorders were also increased.

Because of the pharmacokinetic interaction [see *Drug Interaction (7.3)*] and possible pharmacodynamic interaction, reconsider the need for digoxin therapy. If digoxin treatment is continued, halve the dose of digoxin, monitor serum levels closely, and observe for toxicity.

Calcium channel blockers

Calcium channel blockers with depressant effects on the sinus and AV nodes could potentiate dronedarone's effects on conduction.

Give low doses of calcium channel blockers initially and increase only after ECG verification of good tolerability [see *Drug Interactions (7.3)*].

Beta-blockers

In clinical trials, bradycardia was more frequently observed when dronedarone was given in combination with beta-blockers.

Give low dose of beta-blockers initially, and increase only after ECG verification of good tolerability [see *Drug Interactions (7.3)*].

7.2 Effects of Other Drugs on Dronedarone

Ketoconazole and other potent CYP 3A inhibitors

Repeated doses of ketoconazole, a strong CYP 3A inhibitor, resulted in a 17-fold increase in dronedarone exposure and a 9-fold increase in C_{max} . Concomitant use of ketoconazole as well as other potent CYP 3A inhibitors such as itraconazole, voriconazole, ritonavir, clarithromycin, and nefazodone is contraindicated [see *Contraindications (4)*].

Grapefruit juice

Grapefruit juice, a moderate inhibitor of CYP 3A, resulted in a 3-fold increase in dronedarone exposure and a 2.5-fold increase in C_{max} . Therefore, patients should avoid grapefruit juice beverages while taking MULTAQ.

Rifampin and other CYP 3A inducers

Rifampin decreased dronedarone exposure by 80%. Avoid rifampin or other CYP 3A inducers such as phenobarbital, carbamazepine, phenytoin, and St John's wort with dronedarone because they decrease its exposure significantly.

Calcium channel blockers

Verapamil and diltiazem are moderate CYP 3A inhibitors and increase dronedarone exposure by approximately 1.4- to 1.7-fold [see *Drug Interactions (7.1, 7.3)*].

Pantoprazole

Pantoprazole, a drug that increases gastric pH, did not have a significant effect on dronedarone pharmacokinetics.

7.3 Effects of Dronedarone on Other Drugs

Statins

Dronedarone increased simvastatin/simvastatin acid exposure by 4- and 2-fold, respectively.

Because of multiple mechanisms of interaction with statins (CYPs and transporters), follow statin label recommendations for use with CYP 3A and P-gP inhibitors such as dronedarone.

Calcium channel blockers

Dronedarone increases calcium channel blocker (verapamil, diltiazem or nifedipine) exposure by 1.4- to 1.5-fold [see *Drug Interactions (7.1)*].

Sirolimus, tacrolimus, and other CYP3A substrates with narrow therapeutic range Dronedarone can increase plasma concentrations of tacrolimus, sirolimus, and other CYP 3A substrates with a narrow therapeutic range when given orally. Monitor plasma concentrations and adjust dosage appropriately.

Beta-blockers and other CYP 2D6 substrates

Dronedarone increased propranolol exposure by approximately 1.3-fold following single dose administration. Dronedarone increased metoprolol exposure by 1.6-fold following multiple dose administration [see *Drug Interaction (7.1)*]. Other CYP 2D6 substrates, including other beta-blockers, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs) may have increased exposure upon co-administration with dronedarone.

Digoxin and P-glycoprotein substrates

Dronedarone increased digoxin exposure by 2.5-fold by inhibiting the P-gP transporter [see *Drug Interactions (7.1)*]. Other P-gP substrates are expected to have increased exposure when coadministered with dronedarone.

Warfarin and losartan (CYP 2C9 substrates)

In healthy subjects, dronedarone at a dose of 600 mg twice daily increased S-warfarin exposure by 1.2-fold with no change in R-warfarin and with no clinically significant increase in INR. In clinical trials in patients with AF/AFL, there was no observed excess risk of bleeding compared to placebo when dronedarone was co-administered with oral anticoagulants. Monitor INR per the warfarin label.

No interaction was observed between dronedarone and losartan.

Theophylline (CYP 1A2 substrate)

Dronedarone does not increase steady state theophylline exposure.

Oral contraceptives

No decreases in ethinylestradiol and levonorgestrel concentrations were observed in healthy subjects receiving dronedarone concomitantly with oral contraceptives.

MULTAQ (dronedarone) Tablets

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see *Contraindications (4)*]

MULTAQ may cause fetal harm when administered to a pregnant woman. In animal studies, dronedarone was teratogenic in rats at the maximum recommended human dose (MRHD), and in rabbits at half the MRHD. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

When pregnant rats received dronedarone at oral doses greater than or equal to the MRHD (on a mg/m² basis), fetuses had increased rates of external, visceral and skeletal malformations (cranioschisis, cleft palate, incomplete evagination of pineal body, brachygnathia, partially fused carotid arteries, truncus arteriosus, abnormal lobation of the liver, partially duplicated inferior vena cava, brachydactyly, ectrodactyly, syndactyly, and anterior and/or posterior club feet). When pregnant rabbits received dronedarone, at a dose approximately half the MRHD (on a mg/m² basis), fetuses had an increased rate of skeletal abnormalities (anomalous ribcage and vertebrae, pelvic asymmetry) at doses ≥ 20 mg/kg (the lowest dose tested and approximately half the MRHD on a mg/m² basis).

Actual animal doses: rat (≥ 80 mg/kg/day); rabbit (≥ 20 mg/kg)

8.3 Nursing Mothers

It is not known whether MULTAQ is excreted in human milk. Dronedarone and its metabolites are excreted in rat milk. During a pre- and post-natal study in rats, maternal dronedarone administration was associated with minor reduced body-weight gain in the offspring. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MULTAQ, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother [see *Contraindications (4)*].

8.4 Pediatric Use

Safety and efficacy in children below the age of 18 years have not been established.

8.5 Geriatric Use

More than 4500 patients with AF or AFL aged 65 years or above were included in the MULTAQ clinical program (of whom more than 2000 patients were 75 years or older). Efficacy and safety were similar in elderly and younger patients.

8.6 Renal Impairment

Patients with renal impairment were included in clinical studies. Because renal excretion of dronedarone is minimal [see *Clinical Pharmacology (12.3) in the full prescribing information*], no dosing alteration is needed.

8.7 Hepatic Impairment

Dronedarone is extensively metabolized by the liver. There is little clinical experience with moderate hepatic impairment and none with severe impairment. No dosage adjustment is recommended for moderate hepatic impairment [see *Contraindications (4) and Clinical Pharmacology (12.3) in the full prescribing information*].

10 OVERDOSAGE

In the event of overdosage, monitor the patient's cardiac rhythm and blood pressure.

Treatment should be supportive and based on symptoms.

It is not known whether dronedarone or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis or hemofiltration).

There is no specific antidote available.

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1, rue de la Vierge

33440 Ambares, France

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sanofi-aventis U.S. LLC

Bridgewater, NJ 08807

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VITALS

Major Finding: A total of 34% of available lungs and 45% of hearts were successfully procured from donors managed for more than 20 hours, compared with only 7% of lungs and 12% of hearts from donors managed for 20 hours or less.

Data Source: Prospective study of 100 consecutive donors in a regional organ procurement program.

Disclosures: The study was internally funded. Dr. Christmas disclosed no conflicts of interest.

40 hospitals in a 20-county region. The analysis consisted of data on 100 consecutive donors from 2007 through 2008 that included age, ethnicity, blood type, mechanisms of death, management teams, organs procured, organs transplanted, donor type, donor management, reasons for nonuse of organs, and donor management goals.

Causes of death were traumatic brain injury in 44 donors, cerebrovascular accident or stroke in 38, anoxic brain injury in 13, and other in 5.

The management goals included mean arterial pressure (60-100 mm Hg), central venous pressure (4-10 mm Hg), pH (7.30-7.45), PaO₂ (greater than 100 mm Hg), serum sodium (155 mEq/L or less), serum glucose (less than 150 mg/dL), and urine output (0.5-0.3 mL/kg per hour).

Although heart and lung procurement rates were significantly higher for donors managed for longer times, there were no significant differences between less than 20 hours vs. more than 20 hours in terms of the percentage of kidneys (85% and 91%, respectively) or livers (90% in each group) successfully harvested.

There were also no significant differences between the time groups in any of the preprocurement management goals.

The study was limited by the use of data from a single organ procurement organization, small sample size, and lack of data on the exact time of brain death, Dr. Christmas acknowledged.

The investigators speculated that the longer interval between brain death and organ procurement might permit the improvement of in situ graft function and might promote the procurement of some organs initially deemed unsuitable. ■