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EDITORIAL

WILEY Congenital Heart Disease

Perspective. Digoxin for interstage single ventricle patients: What could possibly go wrong?

In infants born with hypoplastic left heart syndrome (HLHS) and related defects, surgical repair is now offered in essentially all major North American pediatric cardiac centers, most commonly employing three separate stages. While each stage of the Norwood-Glenn-Fontan progression has a discrete risk of surgical mortality, there is also the important problem of mortality occurring between stages 1 and 2. This "interstage mortality" occurs mainly in infants who have been discharged to home following one of the versions of the Norwood procedure, while awaiting the bidirectional Glenn procedure. Most centers have interstage programs designed to follow infants closely at home to allow early intervention in the event of problems such as poor weight gain, cyanosis, intercurrent respiratory illness, and other problems that may be poorly tolerated in these fragile infants. These interstage programs have been credited with substantially reducing the incidence of interstage mortality.[1]

One fascinating development in this story is the recognition of a possible protective effect of digoxin. Brown et al in a study using outcomes data provided through the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) reported on outcomes of 544 Norwood survivors without documented arrhythmias, 22% of whom were discharged on digoxin. They found a lower mortality rate in those discharged on digoxin as compared with those not discharged on digoxin (1.7% vs 9.9%).[2] More or less simultaneously, in a retrospective analysis of data from the Single Ventricle Reconstruction (SVR) trial, Oster et al studied outcomes in 330 infants discharged following stage I Norwood, 31% of whom were discharged on digoxin. They found a 3.5-fold higher mortality rate among infants discharged without digoxin vs those discharged on digoxin (12.3% vs 2.9%). This difference could not be explained by other factors evaluated by the investigators including underlying anatomy.[3]

How might one explain these interesting findings? Both papers' authors note that in most centers there was variability in the percentage of patients treated with digoxin and that it is impossible to know the reasons for the use of the medication in specific patients in these retrospective series. Therefore, possible confounders cannot be completely excluded. Perhaps patients were more likely to get digoxin if they had clinical signs of overcirculation, and overcirculation is a marker for the lack of significant pulmonary vascular disease, shunt obstruction, or venous obstruction. Many other possible explanations can be entertained. However, assuming digoxin actually does exert a protective effect, the biological mechanism of the presumed effect is mysterious. One can hypothesize several biologically plausible explanations. Arrhythmias have never really been implicated in the mechanism of interstage mortality, and I personally doubt that digoxin would provide any substantial protection against potentially fatal atrial or ventricular arrhythmias. The positive inotropic effect of digoxin is well known, and perhaps this plays a role. However, a prominent effect of digoxin is slowing the heart rate. In fact, in the early days of the use of digitalis in adults with congestive heart failure and acute myocardial infarction, a frequently cited reason for the use of digitalis (along with oxygen and morphine) was to slow down the heart rate.[4,5] We know that patients with single ventricle physiology tend to tolerate sinus tachycardia (and other tachyarrhythmias) poorly, likely because tachycardia limits time for coronary perfusion. Perhaps digoxin simply slows the heart and that is a good thing in these marginal infants.

The recognition of the association between digoxin use and lower interstage mortality has led to the widespread practice of starting these infants on digoxin in the hospital and maintaining them after discharge until their second-stage operation. This is despite the fact that this intervention has not been studied prospectively. Is this a concern? Of course it is. It short-circuits the usual progression of clinical research, in which retrospective studies allow for hypotheses that are then tested prospectively. There are many examples of retrospective findings that did not pan out when studied prospectively, and we should be aware of the limitations of observational studies. In our field, we can remember the SVR trial which failed to show a substantial difference in outcomes between the two procedures (Norwood vs Sano) beyond 12 months, despite a number of retrospective single-center reports citing improved outcomes.[6] Similarly, a trial of enalapril vs placebo in infant single ventricle patients failed to show an improvement in growth, heart failure class, or mortality, despite the widespread accepted use of afterload reduction in such patients.[7] More pertinent for this discussion is the experience with hormone replacement in healthy postmenopausal women, for whom multiple observational studies suggested a protective effect against coronary disease.[8] When studied prospectively, however, in the Women's Health Initiative, hormone replacement was unexpectedly found to actually increase the risk of coronary disease as well as of breast cancer and several other conditions.[9] Prospective trials often provide important

information that is unavailable otherwise, and sometimes they change our view completely. Interestingly, the latest data concerning digoxin in interstage patients, recently published by Truong et al using data from the above-mentioned enalapril trial, were unable to demonstrate improved survival in digoxin-treated interstage infants, although there was a nonsignificant trend. However, the use of digoxin was associated with poorer weight gain, a concerning finding.[10]

To be clear, I am not arguing against the use of digoxin in this small group of patients until we have a prospective trial, as such trials may not be feasible given the small numbers of subjects potentially available, and the expense. However, I am arguing that we should be humble and circumspect, and recognize that we may well be wrong.

In truth, my principle concern with the use of digoxin in this patient population is in relation to safety. Deploying a completely benign intervention in the hopes of improving outcomes may seem reasonable. However, digoxin is far from benign. Digoxin is a drug with a very low therapeutic index. The therapeutic index is defined as the ratio of a toxic dose to a therapeutic dose. For drugs like morphine, it is relatively high (70:1) whereas it has been estimated that for digoxin, the dose sufficient to cause death or major adverse effects is only about twice the therapeutic dose.[11]

It is interesting to consider the changes in pediatric cardiology practice that have occurred over the decades. My journey with digoxin began as a fourth-year medical student in 1979, when digoxin was employed in all infants with heart failure, particularly due to shunt lesions, as the first step of medical therapy. The widespread use of digoxin meant that we were all conversant with dosing recommendations at various ages, side effects, expected electrocardiographic changes, rules about redosing after emesis, switching from oral to intravenous and back again, etc. Still, even with that high level of experience, disasters still occurred, related to inadvertent overdosing and lack of recognition of chronic toxicity. Digoxin had essentially disappeared from routine pediatric cardiology practice, for good reason, due to its dangers as well as the recognition of its lack of sustained efficacy for heart failure and the advent of early repair of the most significant shunting lesions. Thus, most current attending cardiologists, fellows, and nurses have little or no experience with this medication.

Digoxin has a very large volume of distribution, with much of the drug distributing to skeletal muscle. Elimination is mainly via direct renal clearance. Various commonly coadministered medications have the potential to increase digoxin levels by interfering with clearance, including spironolactone and various antiarrhythmic agents often employed in HLHS patients. Thus, for any given dose, digoxin levels can rise to toxic levels due to weight loss with loss of skeletal muscle mass, declines in renal function (due to dehydration or use of drugs like captopril), or coadministration of specific medications. The signs of digoxin toxicity can be subtle. While serious or life-threatening arrhythmias such as ventricular tachycardia, ventricular fibrillation, and atrial tachycardia with block are seen particularly with acute overdoses, signs of chronic toxicity are more subtle. These can include irritability, anorexia, and emesis, which are already very common problems in single ventricle infants. One can imagine a scenario in which an infant with feeding difficulty loses weight (and muscle mass) and without a change in digoxin dose, develops chronic toxicity with emesis and more weight loss, creating a vicious cycle. Assessment of digoxin toxicity can also be problematic, as infants can have falsely high levels on radioimmunoassay, due to the presence of endogenous digitalis-like factor.[12,13] Finally, if digoxin toxicity is suspect in an infant who dies in the interstage period, postmortem levels are now known to be unreliable due to postmortem redistribution from the release of the drug from intracellular stores.[14]

What is my conclusion from all of this? Simply, it is a plea for us to respect this drug, and to keep an open mind concerning the importance of its use in this patient population. If we choose to use digoxin, we need to review and be conversant with dosing regimens, coadministered drugs that raise digoxin levels, precautions and signs of toxicity, and be alert for any early signs of toxicity, remembering that they may be subtle and may masquerade as more common manifestations of heart failure in infants. We need to continually remind ourselves that this is one of our most dangerous drugs, and we are using it in our sickest patients.

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