Opinion Paper

‘Digoxin conundrum – Time for validation?’

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ABSTRACT

Despite no incontrovertible data, Digoxin use has been demonised. As a consequence, a lot of patients, stable on Digoxin, have been taken off it and offered alternative drugs. However, there is some light at the end of the tunnel for Digoxin, with the reporting of RATE-AF Trial at the recent European Society of Cardiology Congress. Compared to Bisoprolol, Digoxin use was associated with statistically significantly greater improvements in symptomatology and NT ProBNP levels making Digoxin a first line drug for rate control in permanent AF.

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Once a wonder drug, mainly for use in heart failure and atrial fibrillation, Digoxin has lately been demonised as a killer drug. A leading electrophysiologist from Stanford University, Dr. Turakhia commented in Journal of American College of Cardiology, ‘Perhaps, it is time (we) leave foxglove in the garden and in the history books – and out of the medicine cabinet.’ Another well known cardiologist from Yale, Harlan Krumholz, in a tweet dated July 23, 2019 noted, ‘as use declined, so did hospitalisation for Dig toxicity. So major benefit of the Dig may be achieved by not using it ....’.

The corollary of such irresponsible statements, and infact an aftermath, is that scores of patients, who have been stable on Digoxin for years and decades, are now being shifted over to Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs). Surely, some of this is industry driven, but a major component also accrues from ignorance of evidence - a prime example of throwing the baby with the bath tub. If adequate care is taken for detecting Digoxin toxicity early by looking at and seeking bradycardia, noticing electrocardiographic (ECG) changes and if possible, measuring trough levels of the drug once or twice a year, Digoxin can still be used safely and with salutary outcomes. Obviously patients with renal dysfunction or left ventricular outflow tract obstruction continue to remain prime contraindications. An alternative drug, Amiodarone is not entirely virtuous with potentially permanent and mortality generating lung fibrosis and liver dysfunction as side effects. There is a growing body of evidence that the main sin of digitalis may lie in its cheap prize price and lesser profit margins for the stake holders, besides probably the low therapeutic index.

Unfortunately, a lot of data on Digoxin use is observational and therefore by nature has a proclivity to obfuscation. The only randomised control trial, the DIG Trial, allocating systolic heart failure patients in normal sinus rhythm to Digoxin or placebo was neutral, with both groups showing identical reduction in the primary end point of all cause mortality and a 28% lower admission for heart failure (p < 0.001). The increased mortality, seen with the use of Digoxin in certain observational trials, was attributed to prescription bias, in which sicker patients were prescribed Digoxin and therefore, it was the nature of the disease, rather than Digoxin use, which worsened the outcome. Unfortunately permanent atrial fibrillation (AF) has not got its due, as most studies on AF have been on paroxysmal and persistent AF, which lend to interventions and ablative therapies, which are cash generating – ‘Procedures lead to profits. Where there are profits, there are research dollars.’

However, there was some freshness for AF at the recent virtual European Society of Cardiology (ESC) Congress, with the reporting of RATE-AF Trial, where a beta blocker, Bisoprolol was compared to Digoxin in patients with permanent AF. There was no difference in the heart rate responses or physical functioning at six months. However, improvements in symptomatology, New York Heart Association (NYHA) class and NT Pro BNP levels were significantly greater in the Digoxin arm. The authors concluded, Digoxin may be used as a first line drug for rate control for patients in permanent AF.

This shot in-the-arm for Digoxin assumes all the more significance in a country like India, where the burden of valvular AF of the permanent type is probably higher than the western world and the paying capacity of our patients, for costlier drugs, is limited. Also, in the heat of beta blocker/Amiodarone versus Digoxin debate, one must not forget the salutary role that calcium channel blockers can...
play in the rate control strategy of management of AF. Therefore, what we need is an adequately powered Randomized Controlled Trial (RCT) comparing Beta blockers, Calcium channel blockers, Amiodarone and Digoxin, in a head to head contest, in the setting of permanent AF.

As it stands today, Digoxin still holds ground, albeit with careful usage and as John Mandrola sums it up all beautifully, 'Digoxin may be unfairly villainized, but its use requires effort.'

References