

COMMENTARY

Optimizing digoxin dosage: the long winding road

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'Conclusions of so much moment to the welfare of mankind cannot be formed from the events of a few weeks or months. They must depend on an estimate of the greater number of results, from many cases, under circumstances nearly similar. This is the foundation of experience with every rational man, not only in medicine, but in all reasoning concerning probable evidence. The mischief of precipitate conclusions is nowhere more sensibly felt, than in medical practice' (1).

While earlier clinical use of digitalis is well documented, William Withering is credited with formally introducing digitalis into clinical medicine over two centuries ago (2). With the development of chemical techniques, digitoxin was isolated and characterized from *Digitalis purpurea* and digoxin from *D. lanata*. However, since 1785 digitalis glycosides have been the subject of considerable discussion and experimentation. Perhaps even Ferriar (1799) would have been surprised to find that the optimum use of digitalis would be the subject of considerable debate for over 200 years (1). Introduced for the treatment of the dropsy, it was soon promoted as a treatment for a wide variety of conditions, including mania and pneumonia, with considerable ill-effects (3). The major problem with digitalis is that appropriate dosing is essential given its narrow therapeutic window. As Withering carefully noted, 'The foxglove when given in very large and quickly-repeated doses occasions... slow pulse, even as low as 35 in a minute and, cold sweats, convulsions, syncope and death.'

Two pivotal trials [RADIANCE (4) and PROVED (5)] used an unusual, withdrawal from treatment, design to demonstrate digoxin's efficacy in heart-failure. Patients with New York Heart Association (NYHA) class II or III heart failure and with a left ventricular ejection fraction of 35% or less and

receiving digoxin were randomized to continue with digoxin or placebo for 12 weeks. Although in RADIANCE, the patients also received concurrent angiotensin-converting enzyme inhibitors whereas in PROVED they did not, both studies showed that patients randomized to the placebo group did less well in terms of maximum exercise tolerance and treatment failures. While those results provided some rationale for the continued use of digoxin, they were not powered to detect differences in mortality and the design clearly targeted a specific subgroup of heart failure patients, namely those stable on digoxin. Generalizability of the results was therefore limited. The DIG trial (6) was designed to overcome those short-comings. It randomized patients with ischaemic and non-ischaemic heart failure, stable sinus rhythm and left ventricular ejection fraction of 45% or less; 3397 to digoxin and 3403 to placebo. Both digoxin-naïve patients and patients withdrawn from digoxin were included in the trial. Whereas patients on digoxin had fewer hospitalizations for heart failure and improved quality of life, compared with those on placebo, overall there was no difference in mortality. In fact, there was a small increase in cardiac deaths in the digoxin group, which caused considerable unease given that several studies have shown that inotropic drugs such as ibopamine (7), milrinone (8) and vesnarinone (9) increased mortality in heart-failure in a dose-dependent manner.

The fact that digoxin can have a beneficial effect but may also cause serious harm suggests that it may be critically important to achieve optimum plasma concentration. It is therefore of considerable interest that a retrospective analysis of the RADIANCE and PROVED trials suggested that there was little benefit in increasing dosage to reach blood levels above 0.5–0.9 ng/mL (10). Furthermore, a subgroup analysis of the DIG trial suggested that there was an increased risk of death as the blood level of digoxin was increased even

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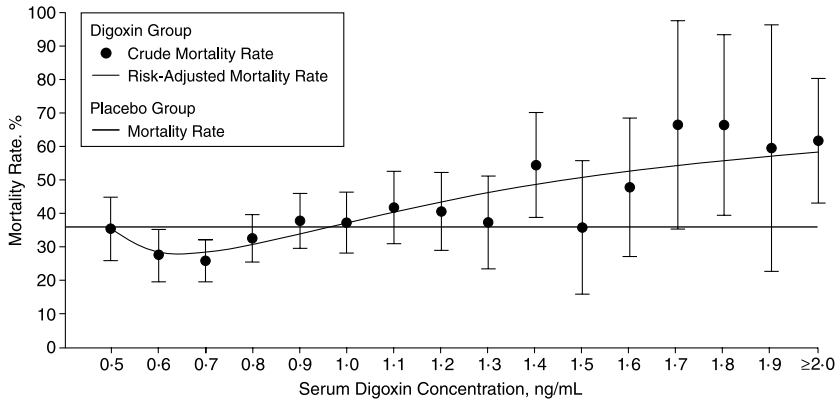


Fig. 1. All-cause mortality rates by serum digoxin concentration groups in Drug Investigation Group trial [reproduced with permission from Rathmore *et al.* (12)].

within the generally recognized therapeutic range of 0.5–2 ng/mL (11). The latest, more detailed, retrospective analysis of the DIG trial data confirmed this finding (12) (Fig. 1).

What then are the implications for practice? Despite the retrospective nature of the analyses (10–12), it would seem prudent to revise the recommended therapeutic range for digoxin to 0.5–0.9 ng/mL, as has already been suggested (Fig. 1). Digoxin is still widely used in general practice and over 4 million prescriptions for digoxin are dispensed annually in the United Kingdom. Given the latest evidence and the fact that digoxin is susceptible to many drug–drug interactions (13) and inadvertent overdosing (14), we advise careful prescribing and periodic blood level monitoring when digoxin is used. As Ferriar (1) further noted, ‘Let me observe, once for all, that nothing is less accurately fixed in medicine, than one of its most important objects, the dose of medicine’.

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