Higher serum digoxin levels were associated with increased mortality in CHF

Rathore SS, Curtis, JP, Wang Y, Bristow MR, Krumholz HM. **Association of serum digoxin concentration and outcomes in patients with heart failure.** JAMA. 2003;289:871-8.

QUESTION

In patients with congestive heart failure (CHF) and systolic left ventricular dysfunction (SLVD) randomized to digoxin or placebo, what is the association of serum digoxin levels (SDLs) with mortality and hospitalization?

DESIGN

Post hoc cohort analysis of a {randomized (allocation concealed*), blinded (clinicians, patients, and outcome assessors),*}† placebo-controlled trial with mean 37-month follow-up (Digoxin Investigation Group [DIG] trial).

SETTING

{302 clinical centers in the United States and Canada}†.

PATIENTS

3782 of the 5281 men who were enrolled in the DIG trial. Inclusion criteria were CHF, left ventricular ejection fraction ≤ 45%, and sinus rhythm. For this analysis, a subset of men in the digoxin group with valid SDLs assessed 1 month after randomization with blood samples drawn ≥ 6 hours after the previous digoxin dose (n = 1171) was compared with men in the placebo group who survived to ≥ 1 month after randomization (n = 2611).

INTERVENTION

Patients in the digoxin group were stratified by SDL at 1 month after randomization: 0.5 to 0.8 ng/mL (n = 572), 0.9 to 1.1 ng/mL (n = 322), and ≥ 1.2 ng/mL (n = 277).

MAIN OUTCOME MEASURES

All-cause mortality. Secondary outcomes included death from cardiovascular causes and death caused by worsening CHF.

MAIN RESULTS

All-cause mortality rates did not differ between placebo and digoxin-group patients overall (P = 0.80). All-cause mortality rates were lower among men who received digoxin with lower SDLs than men who received placebo; men who received digoxin with SDLs ≥ 1.2 ng/mL had higher mortality rates than those who received placebo (Table). Cardiovascular mortality rates were similarly affected.

CONCLUSIONS

In men with congestive heart failure and left ventricular dysfunction, the influence of digoxin varied according to serum digoxin level (SDL), with greater mortality reductions seen at SDLs of 0.5 to 0.8 ng/mL. SDLs ≥ 1.2 ng/mL were associated with increased mortality rates.

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*See Glossary.

†The Digitalis Investigation Group. N Engl J Med. 1997;336:525-33.

All-cause mortality for digoxin (by serum digoxin level [SDL]) vs placebo in heart failure at mean 37 months‡

Digoxin			Placebo	ARR (95% CI)
SDL 0.5 to 0.8 ng/mL	SDL 0.9 to 1.1 ng/mL	SDL ≥ 1.12 ng/mL		
29.9%	—	—	35.2%	5.3% (2.1 to 10.5)
				ARI (CI)
—	38.8%	—	35.2%	2.2% (–3.0 to 8.3)
—	—	48.0%	35.2%	11.8% (5.7 to 18.0)

‡Abbreviations defined in Glossary.

COMMENTARY

The DIG trial (1) showed that digoxin, when given to obtain an SDL of 0.5 to 2.0 ng/mL in patients with CHF and SLVD, reduced death caused by progressive CHF and hospitalizations for CHF. However, no reduction in all-cause mortality or cardiovascular mortality caused by ischemic events and sudden cardiac death was seen. These results relegated the use of digoxin in CHF to second-line therapy for improving symptoms and preventing hospitalizations while angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and aldosterone blockers were used as first-line therapy.

In this post hoc analysis of the DIG trial done in men, Rathore and colleagues showed that an SDL of 0.5 to 0.8 mg/mL was associated with a reduction, an SDL of 0.9 to 1.1 ng/mL had no effect, and an SDL ≥ 1.2 ng/mL was associated with an increase in all-cause mortality. They therefore suggest that the SDL be kept in the 0.5- to 0.8-ng/mL range in men.

The finding that digoxin could have an all-cause mortality benefit has important public health and health care cost implications. However, several issues need to be addressed. First, are the data plausible? While an SDL of 0.5 to 0.8 ng/mL may be optimum for a reduction in mortality, at least in men, one should be cautious in reaching conclusions from a retrospective analysis in which the many complex variables in a patient with CHF cannot be adequately accounted for. For example, an SDL ≥ 1.2 ng/mL may only be a marker of another risk factor. Also, what is the relation of SDL to mortality in patients on both an ACE inhibitor and a β-blocker and possibly an aldosterone blocker? The dose-response relation for mortality might be shifted upwards in patients on a β-blocker or an aldosterone blocker, both of which have been shown to reduce sudden cardiac death in patients with CHF caused by SLVD treated with an ACE inhibitor and a diuretic (2, 3). Furthermore, insufficient data exist about the relation of SDL to mortality in women.

In view of the foregoing uncertainties, how should we use digoxin in a patient with CHF caused by SLVD? I will attempt to maintain an SDL of 0.5 to 0.8 ng/mL when I use digoxin as adjunctive therapy in patients who show signs or symptoms of progressive CHF despite optimal therapy until further prospective data from well-designed trials are available.

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References

1. The Digitalis Investigation Group. N Engl J Med. 1997;336:525-33.
2. **Packer M, Coates AJ, Fowler MB, et al.** N Engl J Med. 2001;344:1651-58.
3. **Pitt B, Zannad F, Remme WJ, et al.** N Engl J Med. 1999;341:709-17.