Are all cardiac glycosides pharmacodynamically similar?

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Cardiac glycosides are used clinically because of two important pharmacological properties, namely positive inotropism in the context of cardiac failure and depression of atrioventricular conduction in the context of supraventricular tachyarrhythmias such as atrial fibrillation.

Although there has been little controversy regarding the clinical value of digitalis in atrial fibrillation doubt has been expressed in recent years about the efficacy of digitalis in patients with cardiac failure in sinus rhythm [1, 2]. However, recent results of prospective clinical studies have shown sustained benefit with digoxin in patients with cardiac failure and in sinus rhythm [3, 4] and digoxin seems to be finding its way back into the treatment of cardiac failure [5, 6].

In the light of renewed interest in digitalis, it seems appropriate to re-examine these two clinically relevant pharmacodynamic properties in terms of the widely accepted notion that all cardiac glycosides are pharmacodynamically similar and that the only differences are pharmacokinetic and therefore only relevant with respect to onset and duration of action. If this notion is true, the general tendency to use digoxin predominantly is acceptable, at least on pharmacodynamic grounds. If, on the other hand, the inotropic properties and effects on atrioventricular conduction of cardiac glycosides can differ from glycoside to glycoside, the tendency to use only digoxin might limit the clinical usefulness of the cardiac glycosides.

Although very little work has been done to examine this issue, there is some evidence to suggest that there are pharmacodynamic differences between various cardiac glycosides with respect to cardiac and extra-cardiac effects. These differences appear to be based on relative water and fat solubilities. Digitoxin is highly lipophilic relative to most other cardiac glycosides, whereas ouabain is relatively hydrophilic; digoxin is somewhere between these two (Fig. 1). Meproscillarin is even more lipophilic than digitoxin and lanatoside C is of approximately the same hydrophilicity as ouabain. In general the presence of hydroxyl groups (polar) enhance hydrophilicity whereas non-polar groups (e.g. methyl groups) enhance lipophilicity. I shall review the evidence for pharmacodynamic differences between cardiac glycosides and shall also discuss the possible clinical implications thereof.

Data from animal experiments

In the mid-seventies Runge et al. published the results of experiments in the intact guinea-pig, which suggested that cardiac glycosides of different polarities might have different pharmacodynamic properties [8, 9]. They used doses of ouabain and digitoxin which produced the same negative chronotropic effect and found that digitoxin had a greater positive inotropic effect, measured as the rate-corrected QS2 interval (QS2c), than ouabain. They suggested that lipophilic cardiac glycosides have greater sympathomimetic effects and hence more positive inotropism. Conversely, hydrophilic cardiac glycosides have greater vagomimetic effects and hence more negative chronotropism relative to positive inotropism. Runge consequently suggested that polar cardiac glycosides would be preferable when treating supraventricular tachyarrhythmias and non-polar glycosides when treating cardiac failure.

Prompted by his findings, we performed similar experiments in intact rats [10], using dp/dt as an index of inotropy and the PQ interval to measure atrioventricular conduction as a more clinically appropriate index of usefulness in supraventricular arrhythmias. We also studied the influence of vagotomy and beta-adrenoceptor blockade, in order to assess the influence of the autonomic nervous system. The dose of cardiac glycoside selected was based on the inotropic response of an increase in dp/dt of approximately 40%.

Our findings are summarized in Fig. 2. We found that at the chosen doses, ouabain and digitoxin produced similar increases in dp/dt, but that only ouabain produced significant suppression of AV conduction (PQ interval pro-
suggests that the effect of digitoxin on AV conduction is masked by the sympathetic nervous system and lends support to Runge's notion that polar glycosides are more vagomimetic whereas non-polar glycosides are more sympathomimetic.

Subsequently, Amlie and Storstein [11] compared the relatively hydrophilic digoxin with digitoxin in terms of inotropic and electrophysiological response in intact dogs and found results consistent with the findings already described. Runge [12] also compared the effects of digitoxin, digoxin, and ouabain in intact cats and found that for doses producing roughly the same inotropic response (QS2c shortening), ouabain produced the greatest and digitoxin the least prolongation of the PQ interval (Fig. 3). He also found that the reduction in heart rate was 19 (8)% with digitoxin, 18 (5)% with digoxin, and 6 (4)% with ouabain. Atropine produced an increase in heart rate of 43 (2)% for ouabain, 33 (2)% for digoxin, and 27 (2)% for digitoxin.

We therefore seem to have strong evidence from four different species that for the same inotropic potential, lipophilic cardiac glycosides cause less depression of AV conduction than hydrophilic cardiac glycosides. This is probably due to greater vagomimetic effects with the former and greater sympathomimetic effects with the latter.

**Human data**

Many early clinical studies compared the effects of various cardiac glycosides in humans, but very little can be concluded from them in terms of current concepts of scientific objectivity [13, 14, 15]. However, one study did suggest that digoxin produces greater slowing of heart rate than digitoxin [15].

In a dose-response study in which they compared the relatively more lipophilic cardiac glycoside meproscillin with digoxin, Alken and Belz [16] found a greater prolongation of PQ time relative to QS2c shortening with digitoxin (Fig. 4). In an earlier study, Belz et al. [17] compared digitoxin with the less lipophilic beta-acetyl digoxin and found that digitoxin produced more T-wave flattening relative to QS2c shortening. As vagal stimulation increases T-wave amplitude and sympathetic stimulation decreases it, it was