LETTERS TO THE EDITOR

Comments on "Cardiotonic Activity of Amrinone-win 40680 [5-amino-3,4'-bypyridin-6(1H)-one]

We note with interest the paper by Alousi et al. (1979) that describes an inotropic effect of amrinone, a non-catechol, non-glycoside agent that has been found to increase myocardial contractility. We wish to report, however, that we have had considerable difficulty in demonstrating a positive inotropic effect of this drug in a variety of animal species.

Measurements of the magnitude of contraction in cultured neonatal rat myocardial cells have failed to demonstrate significant positive inotropy in low (0.5 mM), normal (2.0 mM), or high (5.0 mM) CaCl₂. Our studies of tension developed by avian (chicken) cells, both embryonic and up to one week after hatching, and rabbit and cat papillary muscles only occasionally showed a small positive inotropic effect at drug concentrations of $10^{-4}$ M and above. Perfusion of this drug in isovolumic-contracting hypodynamic porcine ventricles post-hypothermic arrest also did not demonstrate a significant inotropic effect. In these studies we used several batches of amrinone, sometimes made up in solution under anaerobic conditions, at concentrations up to $10^{-3}$ M, taking care that we had not altered the pH of the perfusate. All of these animal preparations exhibited a marked positive inotropic response to catecholamines, and most to cardiac glycosides.

Our results are consistent with the view that the positive inotropic effect of amrinone is neither readily nor consistently detected in the hearts of the animals we tested, requires high concentrations ($\geq 10^{-4}$ M) when it does occur, and is much less than the positive inotropic effect of catecholamines and digitalis glycosides. These results could be attributed to our choice of animal species, or to our failure to control either the stability of the drug or the reactivity of its receptors in the myocardium. Either supports the conclusion that amrinone's mode of action is unique when compared to other cardioactive agents.

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References

Reply to the Preceding Letter

The letter of Dr. Katz et al. was brought to our attention. Since our description of the positive inotropic activity of amrinone on cardiac tissues, several investigators confirmed our findings. Dr. R. Palmer's group (de Guzman et al., 1978; Alousi et al., 1979) demonstrated the inotropic activity of amrinone in isolated rabbit and human atrial strips at doses of 30 to 1000 µg/ml (157 to 243% increase in contractile force). Dr. R. Tanz's group (Onaguluuchi and Tanz, 1979), using rabbit papillary muscle and isolated perfused guinea pig heart, showed dose-dependent increases in cardiac contractile force, (50 to 1000 µg/ml resulted in 20 to 250% increase in force). The stage of animal development seems to be important for the demonstration of amrinone activity. Dr. W. Friedman, University of California at Los Angeles (personal communication) has found that adult sheep atrial strips responded to 5 to 100 µg/ml amrinone with 25 to 150% increase in force while fetal tissues of the sheep were not responsive to amrinone.

As to species variations to the inotropic response to amrinone, we have found the following order of decreased sensitivity to amrinone: dog, cat, monkey, rabbit, and rat. This was also reported by A. Schwartz (Schwartz et al., 1979), who found that cardiac tissues obtained from cat, pig, rabbit, and guinea pig are more sensitive to amrinone than that obtained from the rat. Drs. W.H. Barry and T.W. Smith, Harvard Medical School (personal communication) have demonstrated a modest but significant inotropic effect in cultured heart cells from 10-day-old chick embryos.

It is unquestionable that the species and stage of development of the animal are important for the demonstration of inotropic response to amrinone. Also, the methodology used and the degree of protection of amrinone against destruction before it reaches the tissue is very important. On a mg-base,
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