# Cardiodepressive Effects of Thiomerin: Cardioprotective Attempts with BAL, Ascorbic Acid and Thiamin.* (17503)

ARTHUR RUSKIN AND JOHN E. JOHNSON

*From the Department of Internal Medicine, University of Texas School of Medicine, Galveston, Texas.*

The new mercurial diuretic, thiomerin, (mercaptomerin, N.N.R.) has been studied intensively by several groups of investigators,(1-5) since its introduction by Lehman.(6) His original experiments with cats indicated deleterious intraventricular conduction effects, representing toxicity less than 1/160 that of mercurial diuretics in current use which do not contain the monothiol component. There is evidence that in this mercaptide derivative the toxicity has been reduced without impairing the diuretic efficiency of the mercurial compound,(3) whereas the dithiol—BAL reverses both the toxic and diuretic effects of mercurials.(7) We have previously shown that BAL, ascorbic acid, and thiamin, in that order of efficacy, prevent and partially reverse the deleterious conduction effect of mercuhydrin (meralluride, N.N.R.) and other organic mercurials in the isolated rabbit heart.(8) The purposes of this study were (1) to obtain comparative cardiotoxic and cardiolethal dosage levels of thiomerin and (2) to determine the cardioprotective effects of BAL, ascorbic acid and thiamin used before and after thiomerin in the isolated perfused rabbit heart.

*Methods.* The isolated rabbit hearts were perfused with a modified Locke solution at a constant temperature (37°C) and pH (7.4), and driven at definite varied rates with a thyratron stimulator, as in previous studies.(9) BAL, ascorbic acid, or thiamin, in predetermined amounts,(7) were injected into the tube leading to the aortic cannula either 10 minutes before or 10 minutes after thiomerin. Electrocardiograms corresponding to Lead I were obtained at various rates of stimulation, up to the production of A-V

TABLE I.

Doses of Thiomerin in mg/kg Heart Weight Producing Marked Conduction Delays (50% to 150% in QRS Width) and Rapid (Within 10 Minutes) Asystole in Isolated Perfused Rabbit Hearts.

| | |
|---|---|
| Conduction delays | |
| 8,100 | mg/kg (thiomerin only) |
| 8,300 | " " " |
| 9,200 | " " " |
| 11,000 | " " " |
| 11,200 | " " " |
| 13,500 | " " " |
| 14,000 | " " " |
| 14,600 | " " " |
| 15,400 | " " " |
| 15,800 | " " " |
| 17,300 | " " " |
| 17,700 | " " " |
| 22,200 | " " " |
| Rapid asystole | |
| 43,000 | (after ascorbic acid) |
| 48,000 | (after thiamin) |
| 54,000 | (thiomerin only) |
| 56,000 | (after thiamin) |
| 58,000 | (after thiamin) |
| 61,000 | (thiomerin only) |
| 62,000 | (after ascorbic acid) |
| 68,000 | (thiomerin only) |
| 69,300 | (thiomerin only) |
| 72,000 | (after ascorbic acid) |
| 77,700 | (after thiamin) |
| 88,700 | (after ascorbic acid) |
| 110,000 | (after BAL) |
| 128,000 | " " |
| 143,000 | " " |
| 157,000 | " " |

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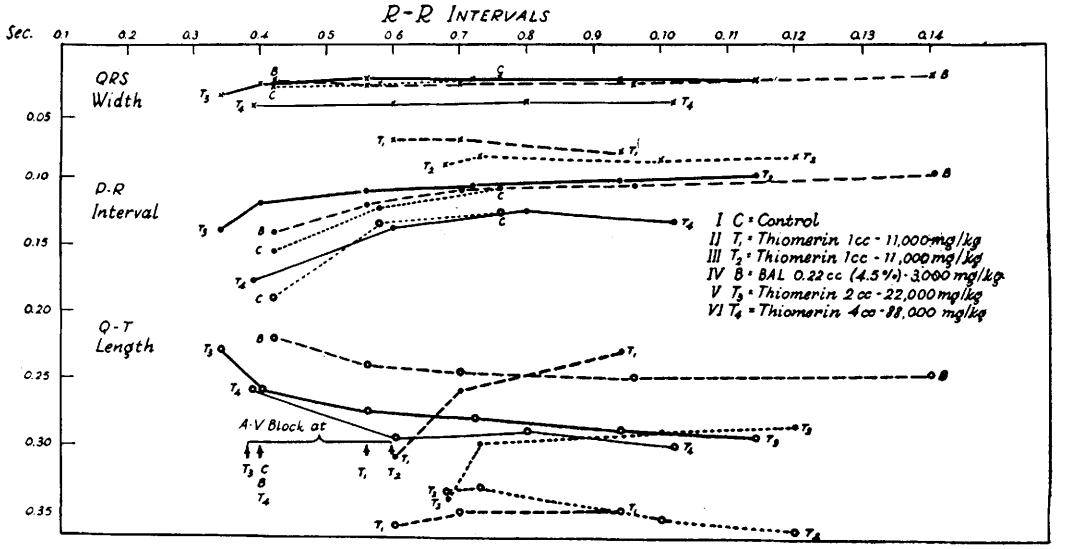


FIG. 1.

Example of usual reversal of thiomerin conduction effects by BAL, and BAL's cardioprotective value. Prolongations of P-R (dots), QRS (crosses), and Q-T (circles) intervals of the electrocardiogram at all rates of stimulation by thiomerin doses equivalent to 22,000 mg of mercury/kg—reversed by BAL. A total of 132,000 mg mercury equivalents per kg tolerated by the heart, with further deleterious but non-lethal conduction effects thereafter.

block, during the control and drug periods and analyzed by the magnifying Cambridge measuring instrument. P-R, QRS and Q-T intervals were then plotted against the R-R intervals for the control and other periods, as curves of recovery. Their prolongation or shortening at various rates of stimulation could thus be graphically evaluated. A total of 31 rabbit heart preparations were tested with thiomerin; 52 previous rabbit heart preparations provided comparative data for other mercurials.(7).

*Results.* 1. *Effects of thiomerin.* Thiomerin, like other mercurial compounds,(1,7) consistently and progressively prolonged conductivity in the ventricles, the atrioventricular conduction time, and the "electrical systole" or Q-T interval. Cardiac dilatation and slowing and lessened contractility resulted from large doses of thiomerin. It produced, to a much lesser extent than other mercurials,(7) monophasic type S-T segment displacements, doming and, rarely, reversals of the T waves. (Older batches of the drug were much more cardiotoxic, just as they showed greater irritation in the subcutaneous and intradermal tissues). Conduction effects were quite marked (prolongations of the QRS intervals of 50 to 150%) with doses of approximately 8,000 to 22,000 mg of mercury/kg of heart weight, with the new lots of the drug. (Older lots were similarly cardiotoxic in doses of 700 to 900 mg/kg). Rapidly (within 10 minutes) cardiolethal doses ranged from 54,000 to 69,000 mg of mercury/kg, with slow idioventricular rhythm and asystole occurring, to the exclusion of ventricular arrhythmias, as a terminal event. Transient ventricular ectopic beats and ventricular fibrillation occurred only once in 31 heart preparations after thiomerin and twice during control runs (rapid stimulation). The above figures indicate a comparative thiomerin cardiotoxicity of less than 1/200 that of mercuhydrin and 1/1,000 those of salyrgan-theophylline and mercuzanthin(7) in the isolated perfused rabbit heart. The cardiolethal ratios of thiomerin to mercuhydrin are less than 1 to 700, and of thiomerin to the other mercurials—1 to 1,800.

*Thiomerin and BAL.* The slight deleterious cardiac conduction effects of BAL in doses of 1800 to 3000 mg/kg have been previously dis-

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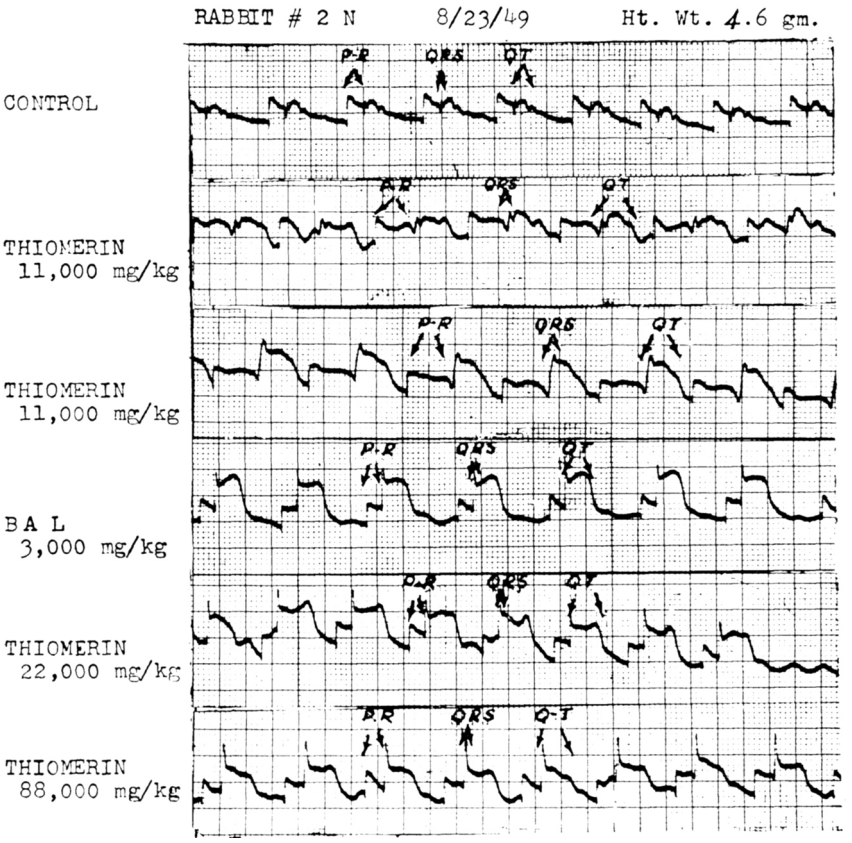


FIG. 2.

Electrocardiograms corresponding to lead I obtained at similar rates of stimulation during control, thiomerin, and BAL periods, 10 minutes apart, for same rabbit heart as in Fig. 1. The shortening of the P-R, QRS, and Q-T intervals by BAL, and their lengthening by thiomerin, much less after BAL than after control runs, are clearly seen.

cussed by us.(7) Thiomerin was tolerated thereafter in doses up to 157,000 mg of mercury/kg of heart weight (Table I), or approximately 2 times the usual cardiolethal dose, when preceded by BAL. BAL, likewise, markedly reversed the prolongation of the electrocardiographic intervals by previous injections of thiomerin into the closed perfusion system (Fig. 1 and 2).

*Thiomerin and ascorbic acid.* Ascorbic acid in doses of 4000 to 6000 mg/kg of heart weight caused slight deformations of the electrocardiographic patterns as previously reported.(7) In contrast to its action in increasing the cardiolethal dosages of mercuhydrin and the more toxic mercurials,(7) it had no such effect in respect to thiomerin (Table I). However, the slight conduction effects of small doses of thiomerin were often partly reversed by ascorbic acid in the above dosage (Fig. 3).

*Thiomerin and thiamin.* Thiamin, in doses of 500 to 1000 mg/kg of heart weight caused slight changes in the electrocardiographic patterns as noted previously.(7) Again, in contrast to its effect on mercuhydrin, it failed to protect against more than the usual cardiolethal doses of thiomerin (Table I). Reversal of deleterious conduction changes resulting from small doses of thiomerin was the exception rather than the rule for thiamin (Fig. 4).

*Comment.* Samples of thiomerin received in the first half of the year 1949 showed cardiodepressive effects corresponding to doses 20 to 25 times those of mercuhydrin (700 to 900 mg/kg vs. 20 to 36 mg/kg respectively). Newer lots of the drug, however, showed a

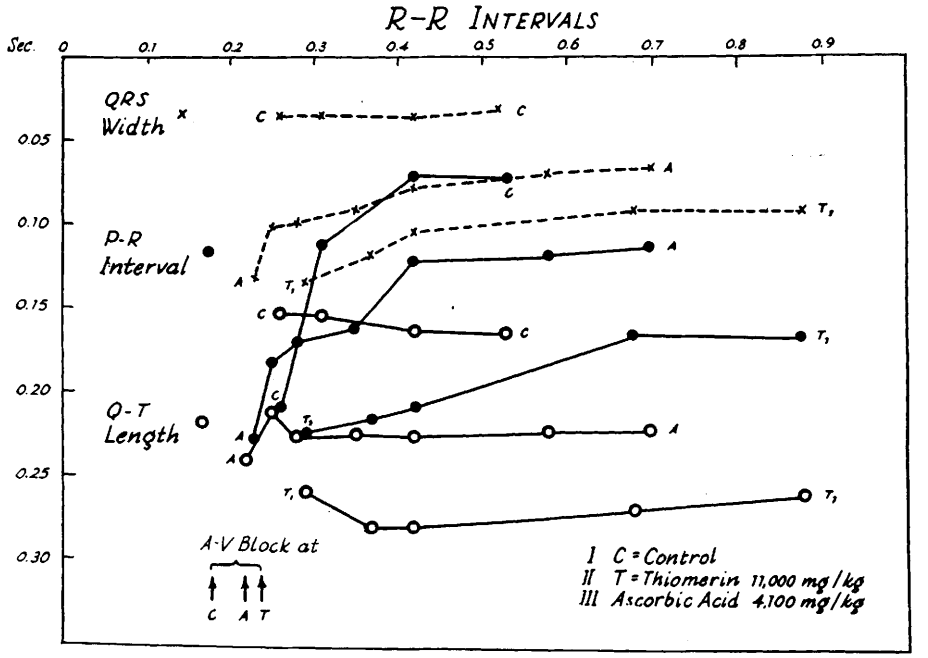


FIG. 3.

Example of frequent reversal of small dose thiomerin conduction effects by ascorbic acid. Prolongations of P-R, QRS and Q-T intervals of the electrocardiogram at all rates of stimulation by thiomerin are reversed, though less markedly than by BAL (Fig. 1), in all instances, by the large dose of ascorbic acid.

cardiac toxicity of less than 1/200 that of mercuhydrin. This ratio corresponds to Lehman's original figure of less than 1/160, measuring the comparative effects of the two drugs in prolonging the QRS interval in cats. Such marked innocuousness of thiomerin from the cardiotoxic standpoint is also emphasized by the absence of ventricular ectopic rhythms in the rabbit heart preparations, or in human subjects(3) given the drug subcutaneously and intravenously. Corresponding absence of marked subcutaneous and intracutaneous irritation both in animal and human subjects(10) of the newer lots of the drug is in marked contrast to the tender subcutaneous nodules and sterile abscesses, and erythematous, papular, vesicular and even necrotic intracutaneous reactions of other mercurials. It is of interest that whereas BAL, ascorbic acid and thiamin raised the maximum cardiolethal (causing asystole within 10 minutes) doses of meralluride to above 10, 7.6 and 2.6 times the M.L.D. of the mercurial alone, respectively,(7) only BAL was successful in increasing the thiomerin tolerance, and that only to the extent of doubling the cardiolethal dosage. We can only speculate as to what the mercaptan linkage has to do with rendering thiomerin less toxic to the cardiac enzyme systems, and BAL of relatively little further cardioprotective effect. Work in progress in our neurochemistry laboratory indicates that oxidation is markedly suppressed or abolished for at least 30 minutes in rat heart slices by mercuhydrin.(11) The depression of respiration of yeast brought about by phenylmercuric nitrate is prevented by cysteine and homocysteine,(12) but more direct biochemical evidence relative to the cardioprotective effects of sulfhydryl compounds is not available. Likewise, the failure of ascorbic acid to in-

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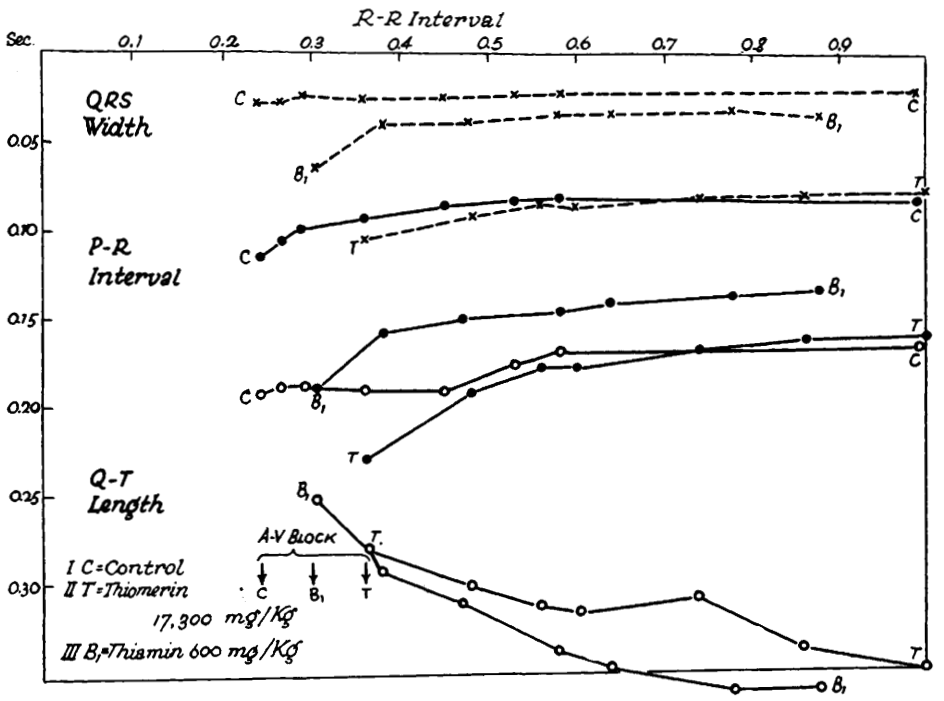


FIG. 4.

Example of infrequent reversal of small dose thiomerin conduction effects by thiamin. Prolongations of P-R and QRS intervals of the electrocardiogram at all rates of stimulation by a moderate dose of thiomerin are reversed by thiamin, as recorded for the three periods 10 minutes apart. The markedly prolonged Q-T intervals resulting from thiomerin are not shortened by thiamin. Compare similar results for mercuhydrin.[7]

crease further the cardiac tolerance of a mercurial compound with a mercaptide linkage may or may not be connected with possible thiomerin potentiation of the already present ascorbic acid in the cytochrome oxidase system in its active reductant state. This cannot be substantiated without further biochemical studies. For what obscure reason thiamin, and presumably its phosphorylated enzyme product — cocarboxylase, increases, though slightly, the cardiac tolerance to organic mercurial compounds other than thiomerin cannot be answered in the present state of our knowledge.

*Summary and conclusions.* 1. In the isolated rabbit heart thiomerin appeared to slow atrio-ventricular and intraventricular conduction and prolong the "electrical systole" (Q-T interval) in doses, as to mercury content, over 200 times those of meralluride, and 1000 or more times those of other commonly used mercurial diuretics. The rapidly cardiolethal dosages bore even larger ratios. Idioventricular slowing and asystole, associated with marked cardiac dilatation and failure of contractility, and not ventricular ectopic rhythms, constituted the lethal manifestations of the thiomerin perfused heart.

2. In contrast to the marked increase in cardiac tolerance to other organic mercurial compounds as a result of preliminary administration of BAL, and to a lesser extent, of ascorbic acid and thiamin, BAL approximately doubled the cardiolethal dosage of thiomerin and the two vitamins were not significantly cardioprotective against the monothiol mercurial.

3. BAL markedly reversed the deleterious conduction effects of even large doses of thiomerin; ascorbic acid did so frequently, after relatively small doses; thiamin reversed the milder effects of thiomerin but in a minority of cases.

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