TITLE : IN VITRO DEMONSTRATION OF THE EFFICACY OF HYDROXOCOBALAMIN IN CYANIDE POISONING

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INTRODUCTION : Sodium nitroprusside (SNP) is a powerful hypotensive agent that has proved useful in the production of controlled surgical hypotension, and the acute management of hypertensive crisis and cardiac failure. Nevertheless, overdosage of SNP may result in cyanide poisoning, since it is the major metabolite of SNP degradation. Among antidotes to cyanide, nitrites and cobalt edetate have toxic side-effects ; sodium thiosulfate, a source of sulfur for hepatic rhodanese, has no such effects but it has been demonstrated that liver damage which results in rhodanese inactivation, does not modify the acute toxicity of cyanide (1). Thus, although sodium thiosulfate actually prevents SNP toxicity, it could be less useful to treat acute cyanide poisoning. Hydroxocobalamin (HOCo) which combines cyanide to form cyanocobalamin, has been demonstrated to prevent SNP toxicity (3), and to be a safe cyanide antidote. We have therefore conducted an in vitro study of the efficacy of HOCo on acute cyanide poisoning.

METHODS : After brief anesthesia with ether, hearts were quickly removed from 18 adults male Wistar rats. Left ventricular papillary muscles were excised and suspended vertically in a Krebs-Henseleit solution (bubbled with 95% O2 - 5% CO2, pH 7.40, 29°C), and field stimulated (0.12Hz). After 1 hr stabilization period at Lmax (i.e., the initial muscle length at the apex of the length-active isometric tension curve), cyanide (NaCN) (10-3 M) was added to the bathing solution. After 10 min, muscles were divided into 2 groups : control group (N=9), and HOCo group (n=9) in which HOCo (10-3 M) was added to the bathing solution ; mechanical parameters were recorded 5 min later in both groups. Mechanical parameters were calculated from 4 twitches : the first twitch was isotonic and loaded with the preload at Lmax ; the second was abruptly clamped to zero-load just after the electrical stimulus ; the third was isometric at Lmax ; the fourth twitch was isotonic and was afterloaded to half-value of the isometric active force at Lmax. The following parameters were recorded : the maximum unloaded shortening velocity (Vmax) by means of the zero-load clamp technique ; maximum lengthening (maxVr) velocity of the twitch with preload only ; isometric active force at Lmax normalized per cross-sectional area (AF) ; an index of load sensitivity of relaxation (ILS) which ranges from about 0.75 in a typical load-sensitive relaxation, to 1 in a typical load-insensitive relaxation. These parameters were chosen because they are very sensitive to hypoxia. Data were expressed as mean (ILS) or mean percent of control values before cyanide ± SD. Comparisons were performed using Student's t-test. $P < 0.05$ was considered significant.

RESULTS : Cyanide poisoning (n=18) induced a decrease in AF (34±15%, P<0.001), Vmax (64±11%, P<0.001), and maxVr (43±14%, P<0.001). The muscles became load-insensitive since ILS increased from 0.77±0.06 to 0.95±0.04 (P<0.001). HOCo induced a nearly complete recovery in AF, Vmax, and maxVr, whereas these parameters remained low in control group (Table). Moreover, the load-sensitivity of relaxation reappeared in HOCo group whereas relaxation remained load-insensitive in control group (Table). The figure shows that papillary muscles recovered beat-to-beat from cyanide poisoning after HOCo.

CONCLUSION : This study confirms that HOCo is a valuable cyanide antidote since a nearly complete recovery is obtained in vitro after severe cyanide poisoning. Moreover, HOCo effects developed very quickly. Because the main toxic target of cyanide is brain cytochrome-oxydase, and because brain damage appears only few minutes after the onset of anoxia, HOCo seems to be the more interesting antidote for acute caynide poisoning.

REFERENCES

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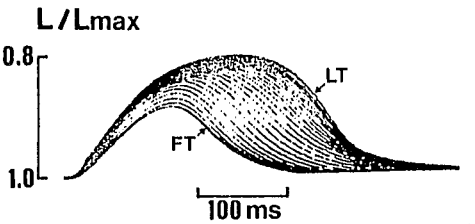

Figure : Rapidity of recovery from cyanide poisoning (first trace : FT) after hydroxocobalamin in a typical papillary muscle. The traces are muscle shortening (L/Lmax) vs time. The last trace (LT) was almost identical to the trace obtained before cyanide poisoning.

TABLE : Evolution of mechanical parameters in control (n=9) and hydroxocobalamin (n=9) groups.

	CONTROL GROUP	HYDROXOCOBALAMIN GROUP	P VALUE
maxVr	44 ± 14	93 ± 17	0.001
Vmax	65 ± 12	91 ± 5	0.001
AF	34 ± 13	90 ± 6	0.001
ILS	0.95 ± 0.04	0.77 ± 0.06	0.001

Data are mean (ILS) or mean percent of control values before cyanide poisoning ± SD. Comparison between groups.