

# Methylene Blue, Nitrites, and Sodium Thiosulphate against Cyanide Poisoning.

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Following the reports of Sahlin,<sup>1</sup> Eddy,<sup>2</sup> Brooks,<sup>3</sup> Geiger,<sup>4</sup> Hanzlik,<sup>5</sup> Hug,<sup>6</sup> and Wendel,<sup>7</sup> we investigated the comparative antidotal action of methylene blue and amyl nitrite in cyanide poisoning and found that methylene blue detoxified 2 M.L.D.'s and amyl nitrite by inhalation 4 M.L.D.'s of sodium cyanide.<sup>8</sup> Amyl nitrite is thus twice as effective as methylene blue. To date we have studied other nitrites and sodium thiosulphate. The last compound has been shown to have an antagonistic action against cyanide by several investigators.<sup>9-13</sup> The results summarized in Table I were all obtained in dogs. It should be noted that nitroglycerine is ineffective as an antidote; while sodium thiosulphate detoxifies 3 M.L.D.'s and so-

TABLE I.

Drug	No. M.L.D.'s of NaCN Detoxified
Nitroglycerine	0
Methylene Blue	2
Na <sub>2</sub> S <sub>2</sub> O <sub>3</sub>	3
C <sub>5</sub> H <sub>11</sub> NO <sub>2</sub>	4
NaNO <sub>2</sub>	4
C <sub>5</sub> H <sub>11</sub> NO <sub>2</sub> and Na <sub>2</sub> S <sub>2</sub> O <sub>3</sub>	10
NaNO <sub>2</sub> and Na <sub>2</sub> S <sub>2</sub> O <sub>3</sub>	13

<sup>1</sup> Sahlin, B., *Skandinav. Arch. Phys.*, 1926, **47**, 284.

<sup>2</sup> Eddy, N. B., *J. Pharm. Exp. Ther.*, 1931, **41**, 449.

<sup>3</sup> Brooks, M. M., *PROC. SOC. EXP. BIOL. AND MED.*, 1932, **29**, 1228; *Am. J. Phys.*, 1932, **102**, 145.

<sup>4</sup> Geiger, J. C., *J. Am. Med. Assn.*, 1932, **99**, 1944.

<sup>5</sup> Hanzlik, P. J., *J. Am. Med. Assn.*, 1933, **100**, 357.

<sup>6</sup> Hug, E., *Compt. rend. soc. biol.*, 1932, **111**, 519; 1933, **112**, 511.

<sup>7</sup> Wendel, W. B., *J. Am. Med. Assn.*, 1933, **100**, 1054; *J. Biol. Chem.*, 1933, **100**, Proc. c.

<sup>8</sup> Chen, K. K., Rose, C. L., and Clowes, G. H. A., *J. Am. Med. Assn.*, 1933, **100**, 1920.

<sup>9</sup> Lang, S., *Arch. Exp. Path. Pharm.*, 1895, **36**, 75.

<sup>10</sup> Heymans, J. F., and Masoin, P., *Arch. internat. pharmacodyn. thér.*, 1897, **3**, 359.

<sup>11</sup> Hunt, R., *Arch. internat. pharmacodyn. thér.*, 1904, **12**, 447.

<sup>12</sup> Voegtlin, C., Johnson, J. M., and Dyer, H. A., *J. Pharm. Exp. Ther.*, 1926, **27**, 467.

<sup>13</sup> Turner, B. B., and Hulpieu, H. R., *J. Pharm. Exp. Ther.*, 1933, **48**, 445.

dium nitrite 4 M.L.D.'s of sodium cyanide. A more striking antidotal effect is exhibited when amyl or sodium nitrite is supplemented with sodium thiosulphate. The combination of the nitrite and thiosulphate does not only show synergistic action but surpasses the sum of their individual values. For example, the number of fatal doses detoxified by sodium nitrite and sodium thiosulphate is 13 instead of 7. It is a definite case of potentiation. Compared with methylene blue, the coupling of sodium nitrite and sodium thiosulphate is  $6\frac{1}{2}$  times as effective. The following protocol is representative of the experiments:

Dog, female, weighing 22 kg., received NaCN subcutaneously at 1:50 p. m., 78 mg. per kg. (13 M.L.D.'s); 1:51 p. m., received intravenously  $\text{NaNO}_2$  22.5 mg. per kg. and  $\text{Na}_2\text{S}_2\text{O}_3$  2 gm. per kg.; 2:00-2:22 p. m. vomited 5 times; 2:23 p. m. drank water; 3:10 p. m. received intravenously  $\text{NaNO}_2$  10 mg. per kg. and  $\text{Na}_2\text{S}_2\text{O}_3$  0.5 gm. per kg.; 3:16 p. m. vomited; 4:53, 7:57, and 9:50 p. m. received intravenously  $\text{NaNO}_2$  10 mg. per kg. and  $\text{Na}_2\text{S}_2\text{O}_3$  0.5 gm. per kg.; 8:15 a. m. of the next day, completely recovered.

To test the crucial efficacy of the nitrite-thiosulphate therapy, dogs were given large amounts of cyanide, say 10 M.L.D.'s, and allowed to develop the cardinal signs of cyanide poisoning such as convulsions, loss of corneal reflex, and failing respiration. As long as there was gasping, the intravenous administration of sodium nitrite and sodium thiosulphate enabled the animals to breathe briskly at once, stand up within a few minutes, and recover completely in several hours.

Hug<sup>14</sup> showed that dogs receiving 6 M.L.D.'s of HCN and rabbits receiving 5 M.L.D.'s of KCN were saved with  $\text{NaNO}_2$  and  $\text{Na}_2\text{S}_2\text{O}_3$ . Buzzo and Carratalá<sup>15</sup> also reported that rabbits could tolerate 18 M.L.D.'s of KCN if  $\text{NaNO}_2$  and  $\text{Na}_2\text{S}_2\text{O}_3$  were injected after the poison; whereas  $\text{NaNO}_2$  alone detoxified 3 M.L.D.'s, and  $\text{Na}_2\text{S}_2\text{O}_3$  alone 10 M.L.D.'s of KCN. The synergistic action of the nitrite and thiosulphate appears to be beyond doubt.

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<sup>14</sup> Hug, E., *Prensa méd. Argent.*, 1933, **20**.

<sup>15</sup> Buzzo, A., and Carratalá, R. E., *Seman. méd.*, 1933, **40**, 1966.