



# Literature Reviews

## Methylene blue added to a hypertonic-hyperoncotic solution increases short-term survival in experimental cardiac arrest.

Miclescu A, Basu S, Wiklund L.  
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### Abstract:

Methylene blue is not just for methemoglobinemia anymore. The blue dye sometimes improves circulation in “dire” situations. Accordingly, researchers in Uppsala report a benefit of methylene blue as an aid to resuscitation from cardiac arrest.

Fifty-nine anesthetized piglets (approximately 25 kg), divided into three groups, were electrically subjected to ventricular fibrillation. After 12 minutes of untreated cardiac arrest, chest compressions and ventilation with 100% O<sub>2</sub> were initiated. The animals received arginine vasopressin and one of three other intravenous therapies: isotonic saline alone (55 ml/kg/hr), hypertonic saline/dextran (7.5%/6%) alone (10 ml/kg/hr), or hypertonic saline/dextran with methylene blue (10ml/kg/hr and 7.5 mg/kg/hr, respectively). Countershocks were attempted after 8 minutes of resuscitation, and, if necessary, intravenous epinephrine was administered.

The hypertonic saline/dextran group fared better than the isotonic saline group (survival of 12/19 versus 9/20 in the 4 hour experiments). However, methylene blue saline/dextran fared even better than isotonic saline (survival of 16/20 versus 12/19,  $p = .03$ ). Early hemodynamics were best in the methylene blue group. Jugular venous levels of neuronal protein S-100 $\beta$ , early jugular venous levels of inflammatory 15-keto-dihydro-PGF<sub>2 $\alpha$</sub> , and systemic levels of myocardial troponin and creatine kinase were lowest with methylene blue.

### Comments:

The tricyclic methylene blue molecule was the first of the phenothiazine chemicals. It was synthesized by Heinrich Caro in 1876 as an aniline-derived dye for textiles. It faded too fast for commercial success in the fabric industry, but it made much history as a histochemical stain, invaluable biochemical reagent, and multipurpose medical therapeutic. Its pharmacological use began in the 1890s when Paul Ehrlich (Nobel

1908) discovered the dye to have useful antimalarial activity. It was thereby probably the first synthetic antimicrobial drug to have reasonable efficacy and safety when used systemically. In the 1920s it proved a dramatic antidote for cyanide poisoning. Tested against many other poisons, it miraculously reversed toxic methemoglobinemia, and this property is the main reason why the drug is well-known to benzocaine-using anesthesiologists today. However, the drug is full of other surprises. For instance, it helps to reverse symptoms of cyclophosphamide-induced encephalopathy and, exotically, those of Jamaican ackee fruit poisoning.

Robert Furchgott, Louis Ignarro, and Ferid Murad each mentioned methylene blue in their 1998 Nobel speeches on the discovery of nitric oxide as the Endothelium-Derived (and drug-derived) Relaxing Factor of blood vessels. The reagent was useful to them as an antagonist of nitric oxide (<http://nobelprize.org>). The antagonism probably involves many mechanisms. For instance, methylene blue inhibits NO synthetase, reacts directly with NO, generates superoxide molecules (which react rapidly with NO), and inhibits guanylate cyclase (the vessel-relaxing receptor for NO).

Consequently, methylene blue therapy has proven salutary in a number of states of pathologically low systemic vascular resistance. For instance, Francis Schneider (Strasbourg) found the drug to sometimes dramatically help to reverse hypotension in septic shock. Similarly, the drug has been helpful in cases of profound “vasoplegia” following cardiopulmonary bypass, and it may have value in the treatment of protamine reactions. It can help in some cases of anaphylactic shock, and it has helped to treat hypotension related to lithium toxicity, ACE inhibition, and hemodialysis.

It is interesting that our drug armamentarium in cardiovascular anesthesiology includes inhaled NO and nitroglycerin as potentially life-saving sources of NO and methylene blue as a potentially life-saving antagonist of NO. It may be necessary to pharmacologically modulate physiological balance by pressure in either direction.

One caveat about this seminal paper in the use of methylene blue as an aid to resuscitation from electrically-induced fibrillatory arrest is that the experimental animals had normal coronary arteries. It will be interesting to see if the nitroglycerin antagonist is also helpful in the setting of ischemically-induced arrest. If so, we will have a new clinical indication to give a blue drug to a blue patient.