Phase II, Randomized, Controlled Trial Of High-Dose N-Acetylcysteine In High-Risk Cardiac Surgery Patients.


Reviewers:
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Abstract:
Pharmacological aids to renal protection are of keen interest in cardiac surgery. Though N-acetylcysteine (NAC) has some value in other settings, researchers in Melbourne, unfortunately, did not find NAC to preserve renal function in cardiac surgery.

Sixty patients planned for CPB were judged to present high risk because of age > 70 years; serum creatinine > 120 umol/L (1.4 mg/dL); NYHA class III or IV; LVEF < 50%; valve or complex or redo surgery; or insulin dependence. In the randomized, blinded, placebo-controlled study, half of the patients received 300 mg/kg of NAC over 24 h, starting after the induction of anesthesia. This substantial dose amounts to about 21 grams, not milligrams, of drug. Both groups were hospitalized for about 8 days. Parameters examined over 5 days included the absolute change in serum creatinine (baseline to peak level); relative change in serum creatinine; peak serum creatinine; the absolute and relative change in serum cystatin C; urine output; need for renal replacement therapy; length of ventilation; and length of stay in the intensive care unit. Only 2 patients required renal replacement therapy, and, intriguingly, they were in the placebo group. However, no statistically significant difference was established in any of the parameters between the two groups.

Comments:
Cysteine is a nutritionally essential, sulfur-containing amino acid. It is present in most enzymes and in the tripeptide glutathione. It is a precursor of taurine (a putative neurotransmitter and a component of Red Bull “energy drink”) and of the bile acid taurocholic acid.

The N-acetyl form of cysteine (termed mercapturic acid because of strong binding to mercury ions) occurs naturally during the breakdown of glutathione. Mercurials and many drugs are excreted in the urine as NAC conjugates (mercapturates) after reaction of the drugs or drug metabolites with glutathione. For instance, compound A of sevoflurane becomes mercapturated.

NAC has several pharmacological applications based on the high chemical reactivity of its sulfur atom. Its reactions with reactive oxygen species and reactive acetaminophen metabolites palliate Tylenol overdose. Reactions with nitrate groups potentiate nitroglycerin. The mechanism by which NAC inhibits contrast-induced nephropathy is not clear but may involve antioxidant action. NAC may have beneficial immunomodulating and anti-apoptotic activities in, for instance, AIDS.

At least the NAC did no harm. Cysteine is so-named because its oxidized form (cystine) can form urinary calculi. NAC might be a bad drug for cystine stone formers. In fact, even though cysteine is an essential amino acid, it is appreciably toxic as an exaggerated dietary supplement. It exhibits CNS excitotoxicity at the NMDA receptor, can inhibit the function of vitamin B6, and is metabolized in part to toxic hydrogen sulfide gas. Therefore, a higher dose than the present “high dose” of NAC is unlikely to be any better.