Pharmacologic Basis for Stability of High Dose Intravenous Ascorbic Acid (HDIVAA) as used by Bastyr University Clinical Research Center (BCRC) and Anderson Medical Specialty Associates

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The pharmacologic stability of vitamins and minerals in parenteral solutions is reasonably well studied and published, but becomes a confusing data set when attempting to apply the available data to particular admixtures.

Our clinical research center is employing a version of a popularly used (1) HDIVAA formula for research purposes with established safety parameters (1,2). This formula is not specifically addressed in the existing pharmacologic data as to stability and administration guidelines, so this document is presented to summarize the available relevant pharmacologic data and to set a basis for safe use of our HDIVAA formula in human subjects.

The study parenteral formulations include ascorbic acid (commercially pH adjusted with sodium hydroxide and or sodium bicarbonate) concentrations from 25 to 150 grams, with additives of magnesium, calcium and potassium all in their chloride salt forms. The addition of these ions in their chloride salt forms was established during an interventional safety trial completed at BCRC (3). Further publication of this data is in progress, and formulae are available per request.

A stability study including ascorbic acid in combination with minerals and other vitamins (4) showed stability over time which was longer when refrigerated:

"Results: The results showed that the methodologies used for assessing the chemical stability of vitamins B1, B2, B6 and C in the formulation were selective, linear, precise and accurate. The vitamins could be considered stable in the formulation during the three days of study if stored at 4°C. When stored at 25°C vitamin C presented instability after 48 h.

Conclusion: The pediatric formulation containing high amount of calcium in the presence of organic phosphate, amino acids, glucose, sodium chloride, magnesium sulphate, pediatric vitamins and trace elements packaged in bag-type trilaminate presented a shelf life of the 72 h, when maintained under refrigeration, between 2°C and 8°C. This shelf life was measured considering the vitamins studied. Further studies are needed including all the vitamins present in this formulation**."* (4)**

Other data shows that vitamin degradation is accelerated in the presence of metal ions due to oxidation (5), which has a great deal of effect on parenteral ascorbic acid. This data is on par with laboratory calibration data for the measurement of ascorbate (versus dihydroascorbate) which establishes that ascorbate is stable in combination with periodic table main group ions but not polyvalent transition ions (9).

"The most significant cause of chemical instability is the oxidation of specific vitamins. The factors influencing calcium phosphate solubility include the commercial amino acid source, the calcium and phosphate salts used, temperature, magnesium concentration, and final volume. Precipitation can be avoided by organic phosphates. Trace element precipitation is most commonly caused by the formation of iron phosphate salts or copper cysteinate in cysteine-containing amino acid infusions. The least stable nutrient is ascorbic acid, which reacts with oxygen, and is catalyzed by copper ions. Oxygen originates from PN ingredients, the filling process, air remaining in the bag after filling, and oxygen permeation through the bag wall. Storage in multilayered bags with reduced gas permeability can protect residual ascorbic acid." **(5)**

This reasonable caution regarding trace mineral additives (as they are transition group elements) and ascorbate, yet not main group elements like calcium, magnesium, potassium and sodium is echoed in other parenteral guidelines (6).

Time based stability studies agree in general that ascorbate in parenteral solutions is best kept under refrigeration prior to administration if the time from preparation to administration exceeds 12 hours (6,7). This in general applies to solutions with ascorbate, and the main group elements. Addition of B-vitamins and transition metal ions can increase the oxidation of ascorbate and significantly reduce its stability (7,8). Based on available data parenteral mixtures containing ascorbate and either B-vitamins and or transition metals should be mixed and administered within the same one to four hour period, and kept in a light protected refrigerated environment (6,7,8).

Conclusions:

Based on the above review of the pharmacologic data regarding parenteral ascorbate we have established our intravenous formulations for maximum patient safety, (3) maximum stability and ascorbate conservation. Our formulations containing ascorbate (commercially pH adjusted

with sodium hydroxide and or sodium bicarbonate), and the chloride salts of potassium, calcium and magnesium fit all safety and ascorbate protection parameters available in the literature as of this time.

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