"EVALUATION OF THE CHEMICAL AND PHYSICAL STABILITY OF SODIUM DICHLOROACETATE, AN ORPHAN DRUG FOR RARE METABOLIC DISEASES"

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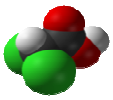

$CHCl_2COONa_2$

V. Cascone[1], A. Tomaino[2], P. Florio[2], M. Cristani[2], G. Rizza[1].
[1]ASP of Ragusa, Hospital Pharmacy, Ragusa, Italy.
[2]University of Messina, Pharmaceutical-biological Department Faculty of Pharmacy, Messina, Italy.

Background

Sodium dichloroacetate (Na-DCA), not patented substance, which is used in the treatment of rare diseases with congenital defects of the piruvate-dehydrogenase-complex (PDHC), produces a marked reduction of acid-base imbalance and lactic acid levels toxic to the brain parenchyma (Fig.1, Fig.2).

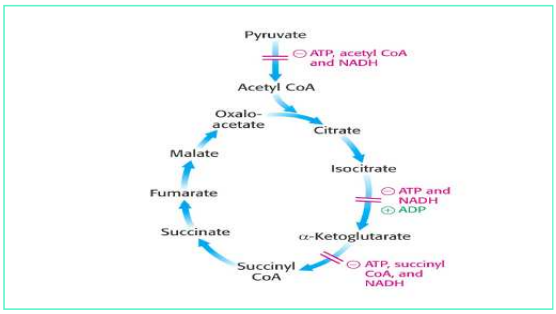

Fig.1 PYRUVATE IN KREBS CYCLE

Purpose

Evaluate the physical-chemical stability of sodium-dichloroacetate in aqueous solution, prepared at our center for a child with mitochondrial cytopathology defect of pyruvate dehydrogenase complex (PDHC) (Fig.2).

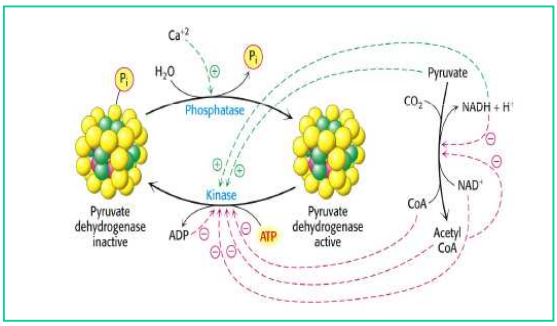

Fig.2 PYRUVATE DEHYDROGENASE COMPLEX (PDHc) [2]

Materials and Methods

Six grammes of sodium dichloroacetate, have been dissolved in 60 ml of water for injections (F.U.I.). Exact concentration of obtained solution has been calculated for extrapolation from a calibration curve, registering absorbance value at the wavelenght of 198 nm of opportune standard solutions (5-50µg/ml) of sodium-dichloroacetate dissolved in water for injections (F.U.I.). The solution has been divided in 3 dark glass containers. The first container has been kept at room temperature (r.t.), the second one in a refrigerator at +4°C, the third one in a freezer at -20°C. The stability of samples, kept at different temperatures, has been monitored at 31, 45, 54, 60 days; for each sample, using appropriate dilution, was registered absorbance values (λ=198 nm), and through calibration curve of sodium-dichloroacetate daily made, was calculated the concentrations of the analyte. The results were expressed as percentage of sodium dichloroacetate in solution (Tab.1).

	Room temperature		+4 °C		-20 °C	
days	average	Standard Deviation	average	Standard Deviation	average	Standard Deviation
0	100	0	100	0	100	0
31	98,01	2,71	99,77	3,51	100,31	2,91
45	96,64	2,19	99,42	1,12	109,43	5,52
54	96,16	3,95	99,52	2,13	114,82	3,67
60	95,89	4,24	99,23	1,74	115,87	4,29

Tab.1 PERCENTAGE OF Na-DCA IN SOLUTION OVER TIME IN DIFFERENT ENVIRONMENTAL CONDITIONS

Results

Samples kept at +4°C are stable during observation period. Samples kept at r.t. show a good stability until to 30 days from preparation, while afterwards we can observe a slow and gradual decay. Samples kept at -20°C show a progressive concentration increase (Fig.3).

Discussion.

The ion dichloroacetate (DCA) stimulates the activity of the enzyme pyruvate dehydrogenase and inhibits its regulatory enzyme pyruvate dehydrogenase kinase 2 (PDHK2). The compound interacts directly with the kinase above and a few years ago was identified the molecular mechanism. The DCA form ionic bonds with residues 382 and 383 of the enzyme (an aspartic acid and a tryptophan, respectively), causing a conformational change in the enzyme and a slowing of its kinetics. Overall, therefore, the DCA decreases the production of lactate. This property was originally used both for studying the metabolism of lactic acid, which to treat situations latticoacidosi. It is also found that the inhibition of PDHK2 improves the performance ventricular cardiac into two experimental animal models. If this is confirmed, the DCA could be used as a supplement therapy in patients with heart failure. It is still ongoing study of the use of DCA as sodium dichloroacetate as an agent for the combustion mitochondrial (apoptosis) of cancer in animal species, having had research about conflicting outcomes [1].

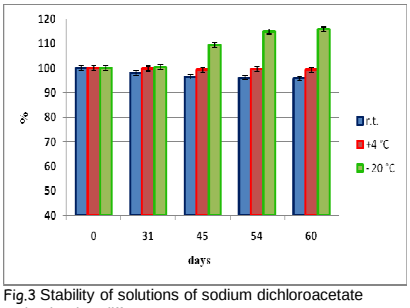

Fig.3 Stability of solutions of sodium dichloroacetate maintained at different temperatures

Conclusions

The observed increase in samples at -20°C can be justified considering the formation of a secondary species with extinction coefficient higher than sodium-dichloroacetate one. Data suggest us that conservation of sodium-dichloroacetate samples isn't opportune at -20°C and at r.t. for more than 30 days.

Bibliography

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contact: dr. valentina cascone
ASP of Ragusa hospital pharmacy
caduti di nassiriya 1 square 97100 Ragusa
Italy valentinacascone@asp.rg.it