Long term use of Carglumic acid in patients with propionic and methylmalonic acidemia

K. Elrfifi, M. Fares, A. Alshah Children hospital/Tripoli

Abstract

Objective: to evaluate the clinical long term use of carglumic acid in cases of propionic and methylmalonic acidemia

Materials and Methods:13 patients diagnosed as PA, MMA at children hospital who are less than 2 years of age with no or minimal brain damage started on carglumic acid 50mg/kg/d divided 12h for at least 3 months were included in this study. Information's were gathered from their medical files at Metabolic OPD during their regular visits and from medical files at paediatric/ ICU admissions if they encountered an acute crisis. Growth parameters, developmental assessment and frequency of admission due to crisis after treatment initiation were studied. In acute decomposition mean ammonia level, biochemical and haematological parameters and mean hospital stay were also observed.

Results: 13 patients included in this study 8 propionic acidemia and 5 methylmallonic acidemia, started on Carglumic acid 50mg/kg/d for a period 3 to 9 months, 3 patients were admitted with metabolic decompensation, with average 2 days hospitalization. **Conclusion**: obvious decrease in no. Of hospitalizations due to metabolic decompensation as well as decrease in duration of hospital stay was noted in treated patients,Carglumic acid is well tolerated with no obvious side effects.

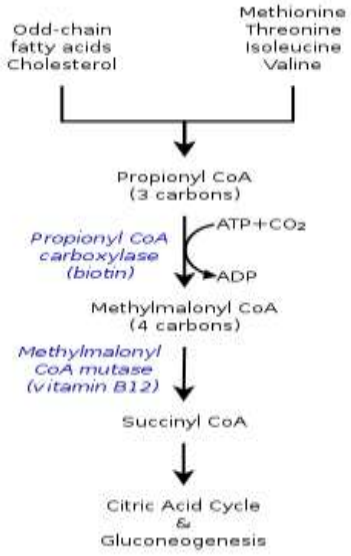
Key words: Carglumic acid, propionic acidemia, methylmalonic acidemia

Introduction:

Prop ionic academia (PA), is a rare metabolic disorder inherited asan autosomal recessive disorder of amino acid and odd-chain fatty acid metabolism, was initially described in 1961, this disease characterized by elevations in glycine in both plasma and urine (1,2). In 1969Hisa et al.were the first who note that there is defective propionate oxidation which is due to Propionyl -Co Acarboxylase (PCC) deficiency. This PCC enzyme catalyse the conversion of proionyl COA to malonyl COA in the mitochondria. Its incidence vary it is more frequent in Saudi Arabia 1 in 2000-5000 live births while in other countries it range from 1 in 50000-100000 (9,10) For methylmalonic acidemia it is from 1:50-100000 live births. 1970 Gompertz et al. describe enzyme deficiency in hepatocytes, and one year after Hsia et al. describe also enzyme deficiency in fibroblasts (3-5). Brandt et

al. in 1974 start treating these disorders with protein restriction(6). Propionic and methylmalonic acidemia both associated with life threatening episodes of hyperammonemia and metabolic acidosis (metabolic crisis) which may cause serious neurological sequels. Neurological complications in PA include seizureswhich take different forms like generalized tonic–clinic, focal (with or without generalization), myoclonic, and atonic seizure. Other neurological complication of prop ionic academia's basal ganglia abnormalities associated with extrapyramidal movement disorders and brain atrophy (7), these neurological abnormalities may be due to cerebrospinal fluid elevations in lactate and ammonia.There is also elevated lactate, glutamine, glycine, and alanine were detected in a patient with neurological symptoms but no signs of catabolism. In the year 2000Chemelli et aldescribeelevations in brain lactate level (lactate peak) on magnetic resonance spectroscopy (8) Other systemic involvement is Bone marrow suppression seen usually in severe metabolic crisis manifested by pancytopeniawhich occurs in some patients during early presentation of the disease (10-12). More rarely is the occurrence of acute pancreatitis (13). Other rare complication as Cardiac complications may occur in prop ionic academia as dilated cardiomyopathy,arrhythmias and long QTC interval(9) Carglumic acid is a structural analogue of N acethylglutamate which is a naturally occurring and selective activator of carbamyl phosphate synthetase. It enhances ammonia detoxification through activation of urea cycle and increase in urea genesis. It is approved in EU since 2003 for treating high ammonia in NAGAS deficiency and in 2014 in USA for treating acute hyperammonemia in organic acidemia (14,15)

Metabolic pathway:



Materials and methods:

A prospective clinical study of 13patients who are diagnosed as PA and MMA at Children hospital/ Tripoli. Inclusion criteria: patients who are less than 2 years of age with no or mild brain damage are included in this study also another 2 patients more than 2 years of age were included as they have multiple admissions with reasonable development and multiple deaths in their families. Patients started on Carglumic acid 50mg/kg/d divided 12 h. These patients are already started on protein restricted diet (0.5-1g/kg/day), also L carnitine 50-100g/kg/d divided 12 hourly, metronidazole 10mg/kg/d alternate day and tonics since diagnosis was made. Data were collected from patients medical files at our out patients clinic, for those who had acute crisis data collected from medical files at ICU / word. The patients were seen monthly at our follow up clinic Data including clinical examination, growth parameter, and developmental asscement, cardiological work up (ECG and echocardiography) is also done before and after starting carglumic acid, parents also asked to report any unusual problem during treatment. For patients admitted with acute crisis mean ammonia levels, biochemical investigations, and also duration of hospital stay were observed. Monthly CBC, biochemistry, LFT, Renal function and lipid profile were done for all patients.

Results

- 13 patients started on treatment, 8 males and 5 females
- 8 patients have PA, of them 5 males and 3 females
- 5 patients have MMA, 3 males and 2 females
- Age at diagnosis range from 1 wk-15m, mean 292 days
- 12 patients have early presentation before 2 months of age,
- 6 patients diagnosed in neonatal period, other 7 patients diagnosed later all of them have an early presentation and admitted before to hospital

Patient& diagnosis	Age at Treatment Start	Age at diagnosis	Sex	Duration of treatment	No. crisis before treatment	No. crisis after treatment

1- PA	21days	21days	M	6m	1	No
2- PA	11m	1 m	F	5m	5	No
3 -MMA	8days	8days	M	4m	1	No
4 -MMA	22days	22days	F	3m	2	No
5- PA	16m	42days	M	4m	2	No
6- PA	13m	6m	M	3m	2	No
7 -PA	5m	5m	M	5m	3	No
8-MMA	3m	2m	F	6m	2	No
9-MMA	2y	16m	F	3m	3	1
10-PA	6m	6m	M	6m	4	No
11-MMA	2y6m	1m	F	3m	10	No
12-PA	15m	15m	M	2m	9	1
13-PA	2y4m	21days	M	9m	10	2

PA=propionic academia MMA= methylmalonic academia m=months
Average time for treatment with Carglumic acid is 4.5months (range 2-9months)

5 patients started on Carglumic acid immediately after diagnosis as they were admitted with metabolic crisis and continued on it (received 3-6m), these patients were admitted with metabolic crisis and Carglumic acid was given initially at high dose 200mg/kg/d then decreased to 50mg/kg/d after crisis passed and continued on this dose.

No. of admissions (metabolic crisis) before and after starting Carglumic acid: 7 Patients with early presentation (before 2 months of age) all except for one had at least one admission before diagnosis average 4 admissions before diagnosis of propionic and or methylmalonic was made, no one had admission during treatmentwith Carglumic acid

Duration of hospital say before and after treatment: average one week (7-10days) before, 2 days after treatment with Carglumic acid

Weight gain during treatment average 0.3 kg/ month for those <1 year of age.

3patients out 13 have crisis during treatment with Carglumic acid

1-Patient number 1 is a Male 4 y+9m diagnosed in neonatal period as propionic academia, family had 3died non diagnosed children, 2 live females, this patient had 10 times admissions because of multiple crisis of hyperammoniemia, 5 of them in the year 2015 all in ICU, he is on protein restriction of 0.6g/kg/day this patients had twice admissions during treatment with Carglumic acid (pneumonia), serum Ammonia was mildly elevated 90-100,

received 9 months Carglumic acid, average hospital stay 2 days. This patient is always sick with too frequent OPD visits, extensive investigations for the possible immune deficiency including viral screen (HIV, TOCHS), immunoglobulin and T- cell functions were all normal.

2-The 2nd patient is a Female 3 years old had 10 admission before and always sick, family has another healthy female child and another died child with the same diagnosis. She has normal development, was admitted with acute tonsillitis after treatment with Carglumic acid, ammonia was normal during admission, this patient received 3 months Carglumic acid.

3-The 3 rd. patient is a Female 16 months old admitted 3 times before one of them in ICU, this patient admitted with severe GE, hypoglycaemia, and dehydration after starting Carglumic acid. Ammonia was mildly elevated, admitted for 2 days, this patient received treatment only for 3 months.

Carglumic acid side effects: only in one patient loose motions were noted by the mother during Carglumic acid treatment.

None of our patients had Cardiological problems before or after starting of treatment with Carglumic acid.

Discussion:

Hyperammoniemia is an emergency situation mostly due to genetic metabolic disorders.One of the most causes of hyperammoniemia are urea cycle disorders and organic acidemia.if left untreated it cause neurotoxicity and irreversible brain damage (16-18), patients with propionic acidemia have life treating episodes of hyperammoniemia (metabolic crisis) as well as intellectual disability also poor growth and stroke episodes of basal ganglia (19).

The administration of N-carbamylglutamate (Carglumic acid) has been reported to be of benefit in many conditions associated with hyperammoniemia, both propionic and methylmalonic acidemia are complicated with hyperammoniemia due to inhibition of Carbamyl phosphate synthesis (first step in urea cycle) leading to reduced synthesis of N-acethylglutamate synthase (NAS) leading to defective ammonia formation (20,21)

Gebhardt, et al were the first who treated patients with hyperammonemia due to Propioncacidemiawith Carglumic acid in acute decompensation and found a

significant increase in ammonia detoxification (22) Carglumic acid is a new drug manufactured byOrphanEuropeCompanywas initially usedto treat hyperammonemia due N-acethylglutamate synthase deficiency (urea cycle disorder). In 2003 first trial of its use in 2 cases one propionic and the 2nd case methylmalonicacademia. It was used to treat acute hyperammonemia in these cases. It has been proven that Carglumic acid when used with or without ammonia scavengers is an effective to restore normal plasma ammonia in hyperammonemic episodes in organic acidemia patients. There are many published guide lines for the use of Carglumic acid in propionic and methylmalonic acidemia during acute decompensation (crises) (23-25) Long term studies of its use for propionic acidemia are still going on in Saudi Arabia where the disease is common 1: 2500 populations but not yet published (26-28). There is a recent published study which is similar to ours (29) and the authors found a decrease in both in number and severity of metabolic crisis in propionic acimeimia although the age group in this study is not similar to ours, as in this study 6 patients their age from 5-22years and only 2 patients are less than 5 years. There is no previous study about propionic and methyl malonic acidemia in Libya.

In our hospital we have 34 patients diagnosed as propionic and methylmalonic acidemia, 28 patients have propionic acidemia (16 alive, 12 died) and 5 patients have methylmalonic acidemia (4 alive and 1 died), these patients have frequent crisis due to viral infections or after vaccinations, and it is the most common cause for admission among inborn errors of metabolism in our hospital (personal observation).

Our patients have high mortality 50% due probably to disease severity and late diagnosis of the disease as there is no national new born screening in Libya yet. All our patients were presented with metabolic crisis at the time of diagnosis.

Mild hperammoniemia sometimes is not recognized by mothers caring such children's at home, these children when started on long term Carglumic acid 50mg/kg/d divided 12 hourly We observed that there was a significant reduction of admissions comparing to before (only 3 patients out of 13 had been admitted in crisis) this may be due to effect of Carglumic acid in decreasing ammonia level which is sometimes raised in the presence of mild upper respiratory infection and prevent the subsequent development of metabolic crises.

During the treatment no major side effects were noted by parents, only one mother noted loose stool.

Although this observation is an important one but we could not do this study for a longer period as Carglumic acid is an expensive medication and also the amount available is not enough to give it for a longer periods.

Long periods of studies are essential to clarify long term use of Carglumic acid in decreasing the frequency of metabolic crises and also its side effects.

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