Peripheral venous route for administration of ammonul infusion for treatment of acute hyperammonemia. *An experience from a tertiary center in Saudi Arabia*

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ABSTRACT

Objectives: To determine the local effects of peripheral Ammonul infusion on the skin and the subcutaneous tissues.

Methods: This retrospective study was conducted at Prince Sultan Military Medical City, Riyadh, Saudi Arabia. All children <16 years of age admitted between December 2015 and October 2018 with hyperammonemia and received Ammonul infusion for treatment were recruited.

Results: Twenty-one patients received the Ammonul infusion. They were admitted 58 times with acute hyperammonemia during the study period, with an average of 2.8 admissions per patient. The mean age of the included patients was 49.5 months. The most frequent underlying diagnoses were propionic acidemia (n=9), urea cycle disorders (n=5), and intrinsic liver disease (n=3). All participants received Ammonul through peripheral lines except 3 who received it through central lines. No extravasation, burns, or other local side effects were observed in this cohort.

Conclusion: This data indicate that the use of Ammonul through a peripheral venous route appears to be safe and not associated with infusion-related local adverse effects.

Keywords: Ammonul, hyperammonemia, sodium benzoate, sodium phenylacetate

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Acute hyperammonemia is a life-threatening condition caused by different inborn errors of metabolism. These include urea cycle defects, organic aciduria, and fatty acid oxidation defects.[1] It may also result from acute hepatic failure where the liver fails to change the lipid-soluble ammonia into the non-toxic, water-soluble urea.[2,3] While the clinical presentation may vary from one patient to another. Acute hyperammonemia can present with a single symptom or a combination of many symptoms, including; nausea, vomiting, altered level of consciousness, seizures, and acute neurological deficit.[4] The severity of the clinical presentation and the prognosis of acute hyperammonemia depends on many factors. These include the age of the patient, the level of the ammonia, and its rising rate. Also, the extent and the duration of the exposure to hyperammonemia plays a major role in the clinical outcome.[2,5] The mainstay of the management of acute hyperammonemia is the use of ammonia scavenger medications. These medications, including sodium benzoate and sodium phenylbutyrate, form an alternative way to get rid of nitrogen precursors.[6,7] Phenylacetate forms phenylacetylglutamine by conjugating with glutamine, while benzoate forms hippurate by its attachment with glycine.[6,8] Both phenylacetylglutamine and hippurate are hydrophilic products excreted in the urine.[3,8] Ammonul is ammonia lowering drug containing both sodium benzoate and sodium phenylacetate. Ammonul was licensed by the United States Food and Drug Administration in February 2005 for use through a central line. Ammonul must be diluted with sterile 10% Dextrose injection (D10W) before administration. Its dilution and dose are determined by the weight and or the body surface area of the patient.[7,9] It is recommended to give it as a loading dose of 250-500 mg/kg over 90-120 minutes and maintenance of 250-500 mg/kg over 24 hours in subjects <20 kg.[7,9] For those above 20 kg, the loading dose is 5.5 grams/m^2 over 90-120 minutes, and the maintenance is 5.5 grams/m^2 over 24 hours.[7,9] The drug is available as 10% injections, and its pH ranges from 6-8.[2] The most common side effects of Ammonul include hypokalemia, hyperchloremia, acidosis, seizures, and respiratory failure.[6] Extravasation of Ammonul may cause local tissue ischemia, burn, and necrosis.[8] Ammonul serum levels may be monitored, especially if its side effects are likely.[8] While the standard practice is to administer Ammonul through a central line, there are limited data on the infusion of Ammonul through peripheral lines. This study aimed to determine the local effects of peripheral Ammonul infusion on the skin and the subcutaneous tissues at the site of infusion.

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Methods. This retrospective observational study was conducted at Prince Sultan Military Medical City, Riyadh, Saudi Arabia. This hospital is a tertiary referral facility for children with inborn errors of metabolism. Inclusion criteria; all children <16 years of age who were admitted with acute hyperammonemia between December 2015 and October 2018 and received the infusion of Ammonul were recruited. All children who did not receive Ammonul infusion were excluded even if they had hyperammonemia. Data were collected from the electronic medical records using a case report form. These data include demographics characteristics of patients, clinical diagnosis, duration of Ammonul infusion, and local side effects. This study was approved by the research ethics committee in Prince Sultan Military Medical City scientific research center.

Statistical analysis. The data were analyzed using Statistical Package for Social Science (SPSS, Version 20). Qualitative data were presented in numbers and percentages. A *p*-value of less than 0.05 was used to determine the level of significance.

Results. Twenty-one patients received the infusion of Ammonul during the study period; 11 were female. The mean age was 49.5 months (range 0.1-166). The underlying diagnoses are shown in Table 1. All inborn errors of metabolism were confirmed by genetic study except for one case, deceased at day 9, that was diagnosed as a case of propionic acidemia based on typical acylcarnitine and organic acid profile (Table 2). The genetic study of the cohort showed different variants; only 2 of them were novel (Table 2). All patients with propionic acidemia have a founder mutation in the PCCA gene,[10] except for one child who had a variant in the PCCB gene (Table 2). Patients in this cohort were admitted 58 times with acute hyperammonemia during the study period, with an average of 2.8 admissions per patient. Ammonul was administered to the patients according to the recommended dilution instructions.[2] Ammonul infusion was given for a total of 126 days during these admissions with a mean of 2.2 days per admission. In all except 3 of these patients, Ammonul was administered through a peripheral line. The mean ammonia encountered at the start of Ammonul was 234.3 umol/l (range 114-609) with a mean level of 99.9 umol/l (range 31-1153) at the discontinuation of the drug. After completion of the Ammonul infusion in all patients except one, the level of the ammonia was below the threshold for dialysis (400 umol/l), and therefore dialysis was not needed. Only one patient with hemochromatosis did not respond to Ammonul infusion and died before dialysis was started with an ammonia level of 1153 umol/l. No extravasation burns or other local side effects were observed in any of the patients included in this study.

Table 1 - Underlying diagnosis of patients presenting with acute hyperammonemi.

Diagnosis	n (%)
Propionic acidemia	9 (42.9)
Methylmalonic acidemia	2 (9.5)
Citrullinemia	3 (14.3)
Arginosuccinic acidemia	1 (4.8)
Carbamoyl phosphate synthetase 1 deficiency	1 (4.8)
Carnitine acyl-carnitine translocase deficiency	1 (4.8)
Pyruvate dehydrogenase E2 deficiency	1 (4.8)
Liver disease	3 (14.3)

Discussion. Ammonul is widely used since its approval by the FDA in 2005 for the treatment of acute hyperammonemia caused by urea cycle defects.[4] Interestingly, in this cohort, propionic and methylmalonic aciduria constituted more than half of the patients who received Ammonul for acute hyperammonemia compared to a quarter of the subjects in our study who had urea cycle defects. This could be explained by the high prevalence of propionic and methylmalonic aciduria in Saudi Arabia. A recent study reported that the incidence of propionic aciduria was 1:14090 and of methylmalonic aciduria 1:15500 in Saudi newborn infants who underwent universal newborn screening.[1] In comparison, an incidence of 1:242741 of propionic acidemia and 1:69354 of methylmalonic acidemia was observed in infants diagnosed by newborn screening in the United States.[11] Furthermore, the phenotype of propionic and methylmalonic aciduria in Saudi patients tends to be severe with frequent metabolic decompensations.[12,13] In a study carried out on 26 Saudi patients known to have propionic academia, 84% had clinical symptoms in the first week and 92% in the second week of life compared to 66% and 80% in an Australian study.[13,14]

The diagnosis of 18 patients in this cohort was confirmed by molecular studies. All variants were previously reported except 2 novel mutations. These novel mutations were in a patient with Pyruvate dehydrogenase E2 deficiency and another subject with progressive familial intrahepatic cholestasis type 3. It is interesting that 7 of the 9 patients with propionic aciduria have a founder mutation in the PCCA gene. Only one patient had a variant in the PCCB gene. This pattern of genotype is in line with the molecular

Table 2 - Characteristics of patients presenting with acute hyperammonemia.

Patient number	Age in months	Gender	Diagnosis	Gene	Variant	No. of admissions	No. of infusion days	Highest NH3 umol/l	Lowest NH3 umol/l	Outcome
1	39	F	PA	*PCCA*	c.425G>A (p.G142D)	15	35	259.7	53	Alive
2	53	M	PA	*PCCA*	c.425G>A (p.G142D)	1	2	249.9	78.1	Alive
3	0.5	F	PA	*PCCA*	c.425G>A (p.G142D)	2	2	141.3	77.9	Alive
4	27	M	PA	*PCCA*	c.425G>A (p.G142D)	6	11	326.2	43.7	Alive
5	58	F	PA	*PCCA*	c.425G>A (p.G142D)	3	6	186.7	66.3	Alive
6	30	F	PA	*PCCA*	c.425G>A (p.G142D)	2	5	251	59	Alive
7	0.3	M	PA	NA	_	1	2	346	137	Deceased 9 days
8	60	F	PA	*PCCA*	c.425G>A (p.G142D)	1	1	160.2	112	Alive
9	5	F	PA	*PCCB*	c.1163T>A (p.L388H)	1	1	179.3	75.6	Alive
10	166	F	MMA	*MUT*	c.329A>G (p.Y110C)	1	2	163.9	65.6	Alive
11	77	M	MMA	*MUT*	c.329A>G (p.Y110C)	1	1	128.6	81.4	Alive
12	58	F	Citrull.	*ASS*	c.470G>A (p.R157H)	2	6	443.7	90.6	Alive
13	96	M	Citrull.	*ASS*	c.470G>A (p.R157H)	6	11	443.1	31.1	Alive
14	81	F	Citrull.	*ASS*	c.470G>A (p.R157H)	2	4	320.3	59.2	Alive
15	108	M	ASA	*ASL*	c.1060C>T (p.Q354X)	1	4	394.2	95.9	Alive
16	14	M	CPS	*CPS1*	c.1759C>T (p.R587C)	3	3	434.7	46.4	Alive
17	9	M	CACT	*SLC25A20*	c.713A>G (p.Q238R)	2	6	305.9	87.4	Deceased at 9 months
18	0.1	F	PDHE2 def.	*DLAT*	c.975G>A (p.P325P)‡	1	1	259.7	96	Deceased 3 days
19	1.5	M	Hemochromatosis	*WES* -ve	_	1	9	1153	203.8	Deceased 45 days
20	111	F	Acute liver disease	*WES* -ve		2	2	245.3	68.4	Deceased at 111
21	72	M	PFIC3	*ABCB4*	c.2088-2092del5 (p.F697fs*)‡	1	2	298	95	Deceased

PA: propionic acidemia, NA: not available, MMA: methylmalonic acidemia, Citrull: Citrullinemia, ASA: argininosuccinic acidemia, CPS: carbamoyl phosphate synthetase deficiency, CACT: carnitine acyl-carnitine translocase deficiency, PDHE2 def.: pyruvate dehydrogenase E2 deficiency, WES: whole exome sequencing, PFIC3: progressive familial intrahepatic cholestasis type 3. ‡the variants were novel

findings reported by Al-Hamed et al[13] in a cohort of Saudi patients with propionic aciduria.

Although not commonly used for hyperammonemia associated with acute liver failure, 3 of our patients received Ammonul aiming to lower the high ammonia. The rate of ammonia decrease was not as good as in urea cycle defects or organic aciduria. Furthermore, one of these 3 patients with fulminant hepatic failure did not respond to Ammonul and died before dialysis was started.

In this cohort, Ammonul was used through the peripheral line in 18 patients; the central line was used only in 3 patients. When Ammonul infusion was commenced, these 3 patients had a prior central line in place for other reasons. As part of our clinical practice guidelines for the management of acute hyperammonemia, we opted to use the peripheral venous route for Ammonul infusion as it secures rapid access to give this drug when needed. Moreover, the insertion of a central line in a child is time-consuming, requires experience, and may sometimes be difficult in emergencies. A recent study showed that implementing a protocol for the use of Ammonul facilitated the management and shortened the time from diagnosis to delivery of Ammonul.[9] None of the 18 patients, who received Ammonul through the peripheral venous line, nor those who received it via a central line, developed any local side effects like extravasation or tissue necrosis. The use of a peripheral line is likely to facilitate the timely administration of Ammonul that helps in the optimum management of acute hyperammonemia.[9] Although no local side effects were observed in the study group, it is highly recommended that the peripheral venous line used for infusion should have an optimum sized vein and to watch the line frequently for signs of extravasation.[2,4,8,9] The latter can be accomplished by applying transparent plaster at the infusion site.

Study limitations. Its retrospective nature and the relatively small number of subjects recruited.

Furthermore, all subjects were treated in a single center. Therefore, further larger prospective studies addressing the use of the peripheral venous line for Ammonul infusion are needed.

In conclusion, we showed that peripheral infusion of Ammonul for the management of acute hyperammonemia appears to be safe and is not associated with infusion-related local adverse effects.

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