

Riana RASAMISON, Jean-Meidi ALILI, Marie-Pierre BERLEUR, Marie-Caroline HUSSON

Regulatory, Pharmaceutical and Medical Department, Pharmaceutical Establishment of Paris Hospitals Group, AP-HP, Paris, France
riana.rasamison@aphp.fr, marie-caroline.husson@aphp.fr

Background and Objective

Arginine (ARG) and Citrulline (CIT) are amino acids both used in hyperammonemia due to urea cycle disorders (UCD), a category of rare disease. ARG is also known to be used for Growth Hormon (GH) stimulation test in adults and children.

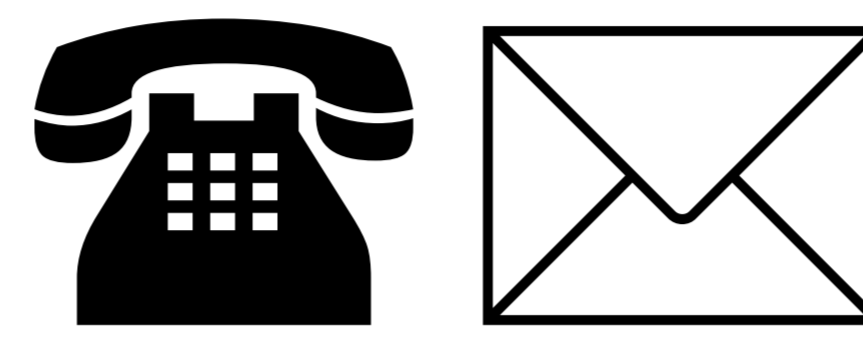
Aim of this work

To study the current therapeutic uses of two hospital preparations of ARG chlorhydrate 6.25 % (w/v) solution for infusion and CIT 500 mg capsules in French hospitals.

Setting and Method

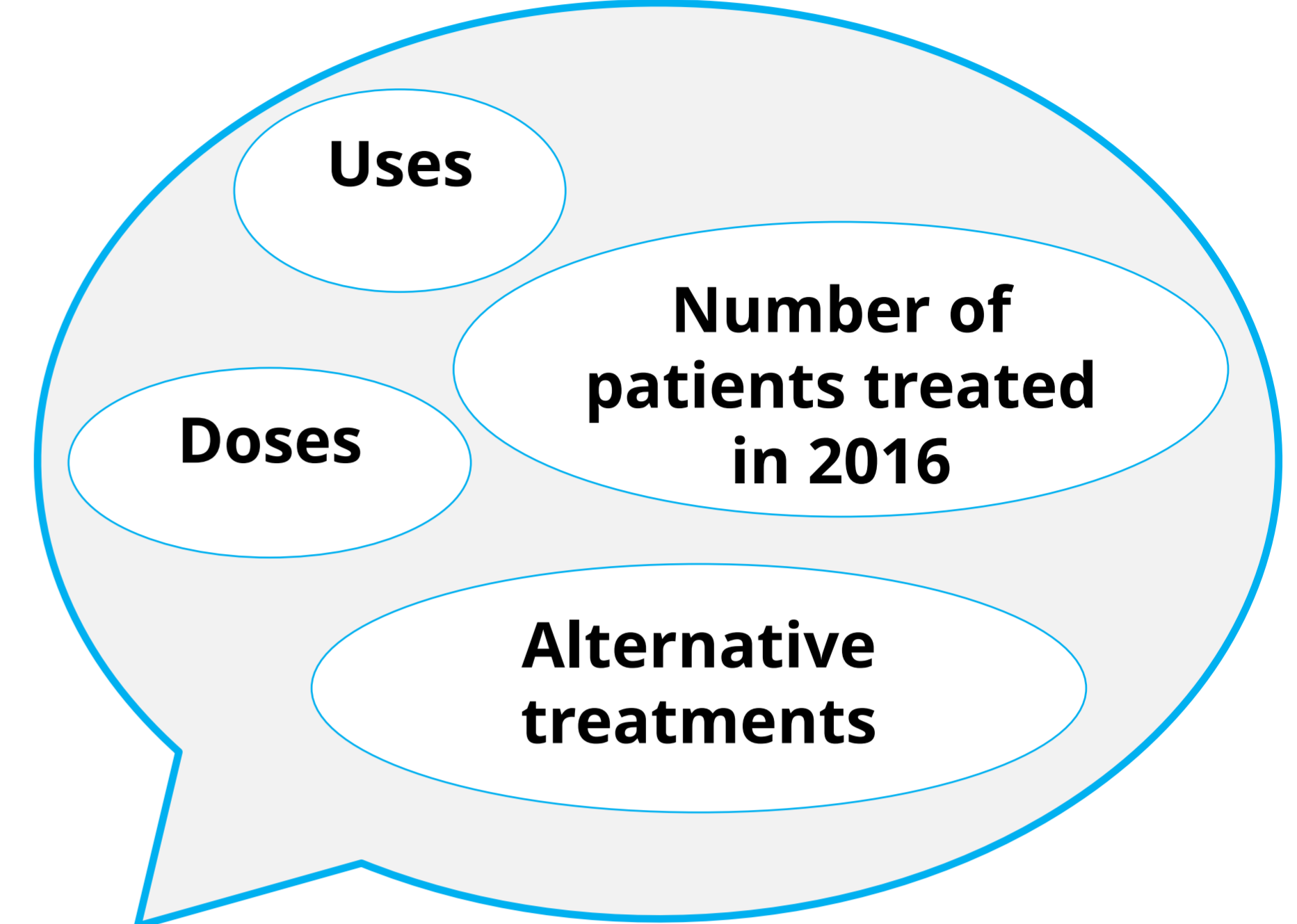
SURVEY

- April-December 2017
- 19 French hospitals
- 9 opened and closed questions



**Pharmacists
&
Clinicians**
(Endocrinology,
Gastroenterology
and
Paediatric wards)

Main outcome measures



Results

Responses received from thirteen hospitals (n=13/19) including 4 reference centers for metabolic diseases (16 pharmacists and 8 clinicians)

ARGININE	5 uses	Doses	Number of patients treated in 2016	Alternative treatments
KNOWN USES	UCD	50 – 300 mg/kg/d (children) 3 – 6 g/d (adults)	260	ARG 21 % solution for infusion (BAXTER)
	Growth Hormon (GH) stimulation test	0.5 g/kg/test max 25 g/test	Not determined	
NEW USES IDENTIFIED	Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS syndrome)	500 mg/kg (children) 10 g/m ² body surface area (adults)	2*	
	Severe metabolic alkalosis	Depend on severity of metabolic alkalosis	2	ARG 21 % solution for infusion (BAXTER)
	Home parenteral nutrition in adult chronic intestinal failure	2 g ARG/bag, 2-6 bags/week	2**	

*Data collected after interviewing one clinician to complete data regarding this orphan disease in June 2018

**Data collected after visiting the pharmacy producing the home parenteral nutrition in December 2017

CITRULLINE	One use	Dose	Number of patients treated in 2016	Alternative treatments
KNOWN USES	UCD	50 – 300 mg/kg/d (children) 3 – 6 g/d (adults)	240	Hospital preparation of capsules of CIT

Discussion

ARGININE The two known uses of ARG in UCD and GH stimulation test are confirmed. Doses are consistent with literature data. Three new uses have been identified.

MELAS syndrome

- Orphan disease
- Mitochondrial cytopathy due to vasodilatation anomaly (lack of nitric oxide) of cerebral arteries¹

This use is recommend by academic societies in mitochondrial cytopathies^{2,3}

Severe metabolic alkalosis

Known use of ARG chlorhydrate⁴

BUT

- Efficacy not established
- Controversial use because of increased intracellular pH and adverse effects⁵⁻⁷

Home parenteral nutrition in adult chronic intestinal failure (eg. short bowel syndrome)

Enteral supplementation of ARG in addition to aminoacid mixtures is expected to stimulate intestinal function and structure^{8,9}

BUT

Specific add of ARG (eg. doses) in HPN is not mentioned in literature data⁸

CITRULLINE

No new use detected. Doses in UCD are consistent with literature data.

Conclusion

- CIT and ARG are essential to treat UCD.
- Effectiveness should be evaluated to confirm if ARG is essential or not in MELAS syndrome, severe metabolic alkalosis and home parenteral nutrition to treat adult chronic intestinal failure.
- Observed doses vary with the therapeutic uses and the severity of the symptoms. They are consistent with literature data.
- This survey should now be completed with the total number of treated patients in France to identify a target population.

1. El-Hattab, *et al.* MELAS syndrome: Clinical manifestations, pathogenesis, and treatment options. *Mol Genet Metab.* 2015;116(1-2):4-12.
2. Koenig MK, *et al.* Recommendations for the Management of Stroklike Episodes in Patients With Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroklike Episodes. *JAMA Neurol.* 2016;73(5):591-4
3. Parikh S, *et al.* Patient care standards for primary mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med.* 2017;19(12).
4. Rothe KF SF. Paradoxical reaction of intracellular pH values during therapy of acid-base imbalance with arginine hydrochloride. *Anaesthesist.* 1983;32:532-7.
5. Martin WJ MG. Treating severe metabolic alkalosis. *Clin Pharm.* 1982;1:42-8.
6. Rothe KF SF, *et al.* Studies on therapy of metabolic alkalosis during experimental uremia. Influences of arginine-hydrochloride on the intra- and extracellular acid-base status of the rat. *Urol int.* 1986;41(3):161-6.
7. Rothe K, Schorer R. Acid-base equilibrium in anesthesiology and operative intensive care medicine. *Physiology, pathophysiology and clinical aspects of alkalosis and mixed disorders.* *Anasth Intensiv Ther Notfallmed.* 1985;20(3):111-8.
8. Pironi L, *et al.* ESPEN guidelines on chronic intestinal failure in adults. *Clinical Nutrition.* 2016;35:247-307
9. Jiang X, Li N, Zhu W, Li J. Effect of enteral supplement of arginine on intestinal adaptation and its mechanism in experimental rats with short bowel syndrome. *Zhonghua Wei Chang Wai Ke Za Zhi.* 2009;12(5):522-5.