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SHORT COMMUNICATION

Anaphylactic shock and lethal anaphylaxis caused by compound amino acid solution, a nutritional treatment widely used in China

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Abstract Compound amino acid solution (CAAS) is a large class of solution of amino acids' mixture and was widely used in China. Its extensive nutritional treatment was accompanied by a substantial incidence of adverse reactions, especially life-threatening anaphylaxis. However, the adverse reactions were reported in isolated case reports only, and the reasons behind this needed further investigation. The Chinese language papers were searched from China National Knowledge Infrastructure and Wanfang database published in China from 1985 to 2010. The search terms "anaphylactic", "anaphylaxis", "allergic", "allergy", "shock", and "adverse reaction" combined with the term "amino acid" were used. Totally 71 episodes of anaphylactic shock and seven deaths in 38 articles were analyzed. Chest distress and cool extremities were the most common clinical manifestations. Almost all patients suffered from significant hypotension. The vast majority of patients were not found to be allergic to certain substances. CAAS was inappropriately administrated in more than one-third of patients. The life-threatening anaphylaxis was prominently prevalent in pregnant women, the elderly and patients with hypersensitivity such as asthma, and patients without medicinal indication. Innovation of processing technique and establishment of more strict supervision system are an urgent need for CAAS to control its production quality and thus improve its safety in China.

Keywords Anaphylactic shock · Compound amino acid solution · Lethal anaphylaxis · Nutritional treatment

Abbreviations

CAAS	Compound amino acid solution
AA	Amino acids

Introduction

Amino acid is one of the basic materials for the life. It is also one of main ingredients for protein synthesis and the nitrogen source to compose all kinds of tissues. Compound amino acid solution (CAAS) is a large class of sterile, nonpyrogenic solution of amino acids mixture, which is consisted of 6–20 kinds of amino acids and sorbitol and sodium bisulfate. CAAS was named according to the number of amino acids, such as CAAS-18 amino acids (AA) which was mainly composed of eight essential and ten non-essential amino acids (Kong et al. 2007). They were widely used clinically in China to supply the nutrition, enhance the immunity, and renew the physiological function, and make the wound healing and make the body recovery (Wang 2010). The productions of amino acid solutions were more than 144 million bottles, accounting

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for 2.18% of the total yields of solutions in China in 2005 (Kong et al. 2007). This extensive nutritional treatment was accompanied by a substantial incidence of adverse reactions, especially life-threatening anaphylaxis (Wang 2010). However, the adverse reactions were reported in isolated case reports only, and the reasons behind this needed further investigation.

Materials and methods

We searched China National Knowledge Infrastructure and Wanfang for Chinese language papers. We used the search terms "anaphylactic", "anaphylaxis", "allergic", "allergy", "shock", and "adverse reaction" combined with the term "amino acid". We have collected all 141 articles about severe anaphylaxis published in medical journals in China from 1985 to 2010. The anaphylactic shock and deaths from anaphylaxis caused by CAAS were analyzed. All these cases were diagnosed by clinical manifestations after intravenous CAAS or post-skin testing or drug allergy history, and the patients showed typical clinical symptoms of anaphylactic shock such as a sudden drop in blood pressure, for which the possibility of contaminated (toxin-, bacteria-, or micro-organism-related septic shock) and fluid overload (congestive heart failure) were excluded.

Results and discussion

These 38 articles (Supplementary material) reported 71 episodes of anaphylactic shock and seven deaths from anaphylaxis caused by CAAS (Chen and Luo 2001; Lu 1993; Luo and Luo 2008; Yan 2001; Yang 1992; Zhao and Zhang 2007). The indefinite kinds of CAAS inducing seven lethal anaphylaxis incidences were not described in the literatures except two cases received CAAS-18AA and CAAS-6AA, respectively. The patients' ages ranged from 27 to 67 years (Table 1). They were hospitalized for tuberculous pleurisy ($n = 2$), hyperthyroidism ($n = 1$), esophageal cancer ($n = 1$), pulmonary infection ($n = 1$), liver cirrhosis ($n = 1$), and 36 weeks gestation ($n = 1$). When allergic reactions to CAAS occurred, epinephrine was injected immediately; however, it failed to save their lives. Especially, a 28-year-old pregnant woman at 36 weeks gestation with fetal growth restriction and no history of drug allergies presented with anaphylactic shock just 15 min after CAAS. Although she was rescued by timely anti-shock treatment, the fetus died of intrauterine distress and neonatal asphyxia initiated by anaphylactic shock. The interval between CAAS and the time of death ranged from 30 min to 30 h (Table 1).

Table 1 Seven cases of fatal anaphylaxis caused by CAAS in China

Reference	Sex	Age (years)	Allergy	CAAS	First use	Presenting condition	Post-CAAS symptoms	Onset of symptoms	Diagnosis	Timely epinephrine	CAAS to time of death interval
Yan (2001)	M	67	Yes	18AA	No	Esophageal cancer	CD, FC, H, N, PS, UC, UI	15 ml	Anaphylactic shock	Yes	88 min
Lu (1993)	F	50	None	–	Yes	Hyperthyroidism	FC, FT, H	5 min	Anaphylactic shock	Yes	40 min
Chen and Luo (2001)	F	27	None	–	No	Pulmonary tuberculosis	PR, SR	100 ml	Exfoliative dermatitis/drug-induced hepatitis/myocarditis/gastrointestinal hemorrhage	Yes	<24 h
	F	40	None	–	Yes	Pulmonary tuberculosis	FT, H, UC	–	Anaphylactic shock	Yes	<24 h
Luo and Luo (2008)	F	51	None	–	Yes	Pulmonary infection	CD, DH, FC, H, HS, LC, T, UC	5 min	Anaphylactic shock	Yes	2 h
Yang (1992)	M	63	None	6AA	Yes	Liver cirrhosis	C, HF, H, LC	10 min	Anaphylactic shock	Yes	30 min
Zhao and Zhang (2007)	F	28	None	–	No	36 weeks pregnant	AP, C, N, V, H, HF	15 min	Anaphylactic shock, intrauterine distress, neonatal asphyxia, aspiration pneumonia	Yes	30 h

– Data not shown, *AP* abdominal pain, *C* chill, *CAAS* compound amino acid solution, *CD* chest distress, *CE* cool extremities, *D* diarrhea, *DH* dysphoria, *DIC* disseminated intravascular coagulation, *F* female, *FC* facial cyanosis, *FT* fainting, *H* hypotension, *HF* high fever, *HS* hyperspasmia, *LC* lip cyanosis, *M* male, *N* nausea, *PR* pruritus, *PS* profuse sweating, *SR* skin rash, *T* tachypnea, *UC* unconsciousness, *UI* urinary incontinence, *V* vomiting

Among the 71 anaphylactic shock cases, all patients were given an IVI. The types of CAAS given were as follows: 6AA ($n = 26$), 18AA ($n = 17$), 17AA ($n = 6$), 19AA ($n = 1$), 15AA ($n = 1$), 11AA ($n = 1$) and the others that data were not shown ($n = 19$). Their ages ranged from 6 months to 78 years (mean 55.7 years), and gender ratio was 1 male to 1.16 females. The primary diseases were shown in Table 2. The anaphylactic shock in these literatures was confined to CAAS as they developed abnormalities several seconds to 2 h after receiving the intravenous dose the drug, resolved following the removal of the drug and the treatment of anti-anaphylaxis and anti-shock. Although a few cases were given any other medication prior to CAAS, there was a re-challenge with CAAS associated with recurrence of anaphylactic shock. Chest distress and cool extremities were the most common clinical manifestations. Almost all patients suffered from significant hypotension. Only 25 cases manifested as pruritus or skin rash.

Among the 71 patients, 9 patients were given CAAS at their own will, without a doctor's prescription. Moreover, CAAS was inappropriately administrated in more than one-third of patients. Twenty-five patients showed no allergic reaction after intravenous CAAS, but then presented with anaphylactic shock when receiving another solution(s). Definite history of drug allergies was only shown in four cases, and there were two cases of tuberculous pleurisy and two cases of bronchial asthma which might be associated with hypersensitivity, and the vast majority of patients were not found to be allergic to certain substances. In one case, a 51-year-old woman with pulmonary infection showed no allergic reaction, but then presented with anaphylaxis just 5 min after receiving the injection and died of anaphylactic shock caused by CAAS. Strikingly in another case, her elder brother of the same parents, a 74-year-old man with no history of drug allergies was seeking treatment for respiratory tract infection when he suffered severe anaphylactic shock just 10 min after receiving intravenous CAAS. He was rescued by epinephrine within 10 min. All 65 patients, including four cases of pregnant women, were rescued without sequelae.

Table 2 The primary diseases for CAAS treatment in 71 cases of patients

Primary disease	*n*
Liver disease	
Acute or chronic hepatitis	22
Liver cirrhosis	4
Cardiac and pulmonary disease	
Respiratory tract infection	5
Coronary heart disease	3
Tuberculous pleurisy	2
Bronchial asthma	2
Digestive system disease	
Abdominal pain	2
Acute or chronic cholecystitis	2
Acute or chronic gastroenteritis	2
Esophageal cancer	1
Upper gastrointestinal bleeding	1
Acute pancreatitis	1
Endocrinopathy	
Hyperthyroidism	1
Diabetes mellitus	1
Others	
Hypodynamia	11
Pregnancy	4
Surgery	3
Injure	1
Hydrogen sulfide poisoning	1
Cerebral hemorrhage	1
Schizophrenia	1

The CAAS is currently used clinically to supply the nutrition, enhance the immunity, and renew the physiological function, and make the wound healing and make the body recovery in China. This extensive nutritional treatment was accompanied by a substantial incidence of adverse reactions, especially life-threatening anaphylaxis (Wang 2010). In this study, the anaphylactic shock was confined to CAAS as they developed abnormalities several seconds to 2 h after receiving the intravenous dose the drug, resolved following the removal of the drug and the treatment of anti-anaphylaxis and anti-shock. Although a few cases were given any other medication prior to CAAS, there was a re-challenge with CAAS associated with recurrence of anaphylactic shock. Even more important, the anaphylactic shock was not confined to CAAS unless the possibility of contamination and fluid overload was excluded.

Among the 71 patients, 9 patients were given CAAS at their own will, without a doctor's prescription. Moreover, CAAS was inappropriately administrated in more than one-third of patients. This is an astonishingly strong effect. In China's western regions, actually, the role of CAAS in nutrition support was exaggerated, and it was abused by some people to boost their immunity against disease and even barefoot doctors who received minimal basic medical and paramedical training and worked in rural villages in China. The unreasonable application of CAAS occurs most of frequently in respiratory tract infection and pregnancy, as shown in Table 2.

The package insert provided by the manufacturer for the amino acid solution lists "hypersensitivity to one or more amino acids" a contraindication to its use. In addition to these manufacturers' warnings, a survey of the entry

"parenteral nutrition (PN)", "amino acid solution" combined with the term "adverse effects" and "hypersensitivity" in PubMed and Embase from 1985 to the present revealed some publications implying an allergic or anaphylactic reaction to PN. In our literature search, we found that most components of PN included mixed amino acid solutions which had already been shown to cause hypersensitivity reaction (Bullock et al. 1990; Huston et al. 2009; Levy and Dupuis 1990; Nagata 1993; Pomeranz et al. 1987; Smolinske 1992). Pomeranz et al. (1987) reported that a 4-year-old child developed an anaphylactic reaction to the amino acid solution (Travasol A, Baxter Healthcare Corporation, Deerfield, IL, USA) as well as the multivitamins and magnesium sulfate solution, which was demonstrated by dermal allergy tests. More recently, Huston et al. (2009) described a case of PN hypersensitivity in a 37-week-gestation infant with congenital diaphragmatic hernia complicated by bowel necrosis and functional short bowel syndrome. The reactions were confirmed with a positive rechallenge. After the amino acid solution (TrophAmine 10%, B. Braun, Irvine, CA, USA) was replaced with a non-bisulfite-containing product, the infant was able to continue to receive intravenous nutrition support without recurrence of symptoms. When an allergic reaction is suspected, however, it is difficult to isolate and identify the specific allergen(s) because there may be more than components responsible for the hypersensitivity reaction. Market et al. (1998) reported a case of anaphylactic reaction to PN in a 4-year-old child when PN was resumed after a 5-day interruption in therapy. Skin-prick response to the multivitamin was slight and negative to the amino acid solution, and thus, the allergic potential of these two PN components individually may not have been significant enough to cause anaphylaxis, but taken together, the allergic potential may have been amplified. Since individual amino acids are unlikely to stimulate an allergic response, the possibility of aggregated amino acids as a potential sensitizing agent cannot be ruled out in these reported cases.

Because CAAS is a compounded product mixed from multiple additives, it is important to maintain alignment with international standards. The sulfites or other preservatives (e.g., butylated hydroxyanisole, butylated hydroxytoluene, polysorbate emulsifiers, and others) are most likely to contribute to the development of severe allergic reactions to amino acid solutions (Mei et al. 2004; Strauss and Koniaris 1998). Sodium bisulfite, one of sulfiting agents and antioxidants, is added to CAAI to decrease the oxidation of amino acids. Considering the limitation of manufacturing technologies, however, most of manufacturers selected sodium bisulfate as antioxidants in China. Recently, the China State Food and Drug Administration (SFDA) recommended that the acceptable daily intake of sodium bisulfate in amino acid infusion was below 0.1%, which was controlled below 0.02% in the developed countries (Mei et al. 2004). Up to now, there is no National Standard of the People's Republic of China on the threshold of antioxidants in CAAS. It is clear that sulfites are not safe preservatives (Levine et al. 1985). Sulfite sensitivity occurs more commonly in patients with asthma. Control of the content of sodium bisulfate in the solution to the maximum extent would be very helpful in reducing adverse effect induced by CAAS. Allergic reactions occurred from sorbitol, another ingredient raised the utilization rate of CAAS, have not been reported.

With the more and more case reports on adverse reactions of CAAS, great attention should be paid. On the one hand, the quality of CAAS was affected by numerous factors, such as manufacturing equipment, raw material, packaging container, and manufacturing techniques. In these English literatures, we searched almost all hypersensitivity reactions to amino acid solutions that were reported in the past two decades, but with continuous improvement of manufacturing process, especially the advent of sulfite-free amino acid solutions; associated adverse effects were reported more infrequently in the developed countries. In China, there were hundreds of CAAS manufacturers, but manufacturing conditions and quality control differed from factory to factory. On the other hand, in the underdeveloped area of China, the role of CAAS in nutrition support was exaggerated, and it was abused by some people to boost their immunity against disease. Finally, quick intravenous infusion and hypersensitivity may also be responsible for the allergic reactions induced by CAAS (Wang 2010). Therefore, the China SFDA included CAAS into the list of solutions with severe adverse drug reactions in August 2007 (The China State Food and Drug Administration 2007a). Innovation of processing technique and establishment of more strict supervision system is an urgent need for CAAS to control its production quality and thus improve its safety in China. The good news is that to provide scientific evidence for government policy, the SFDA has entrusted Sino-Swed Pharmaceutical Corp. Ltd. with parametric release and sterility testing release of CAAS from July 1, 2007 to June 28, 2010 (The China State Food and Drug Administration 2007b). The Chinese National Standard for CAAS was expected to establish in the near future.

Conclusion

In summary, our findings suggest that CAAS should be carefully given to pregnant women, the elderly and patients with hypersensitivity such as asthma, and not used for patients without medicinal indication. Consideration

should be given to using alternatives to sulfiting agents. In the interim, an allergen-warning label should be added to the product, and likewise indications of medication must be strictly controlled.

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