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DESCRIPTION CN101049500A

10 A kind of amino acid composition

[0001]

14 technical field

[0002]

18 The present invention relates to an amino acid composition.

[0003]

22 Background technique

[0004]

26 The progress of modern science and technology can make many diseases get satisfactory treatment, but the malnutrition of clinical patients still exists, accounting for about 50% of the inpatients, and the main manifestation is protein energy malnutrition.

[0005]

32 Protein is the main component of all living cells and body fluids, and is the material basis for maintaining the growth, development, and tissue repair and renewal of the body.

34 Amino acids are the basic units that make up proteins. There are 20 kinds of amino acids that normally make up proteins in the human body.

36 These include 8 essential amino acids and 12 non-essential amino acids, the former including: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, the body cannot synthesize or the

synthesis rate cannot meet the needs, and must be supplied by food; the latter can be synthesized by itself in the body, but in the state of high catabolic stress such as disease, trauma and infection, some non-essential amino acids such as arginine and glutamine Amide, taurine, etc., its demand is greatly increased, exceeding the synthesis capacity of the body, reducing the content of the body, resulting in a decrease in protein synthesis, affecting the immune function of the body, especially under the condition of being unable to eat, it is necessary to try to supplement it, so are called conditionally essential amino acids.

[0006]

⁴⁷ The patient is deficient in protein due to digestive absorption disorders caused by gastrointestinal diseases; or the protein consumption is enhanced due to surgical trauma and burns; or hypoproteinemia is caused by certain diseases; or amino acids must be increased due to malnutrition before and after surgery The supply of nitrogen can make the body achieve a positive nitrogen balance, and promote wound healing and physical recovery; or due to loss of appetite caused by wasting diseases or cancer chemotherapy, it is necessary to supplement protein intake, and the supplement of compound amino acids plays a key role.

[0007]

⁵⁶ After severe trauma, the patient is prone to continuous weight loss, negative nitrogen balance, decreased plasma total protein and albumin levels, accompanied by abnormal changes in plasma amino acid profile, and the synthesis of basic components of small intestinal mucosa (intestinal mucosal protein) is inhibited and normal. Structural damage; immune function suppression (spleen lymphocyte transformation rate and stimulation index decreased, thymus organ index decreased); antioxidant capacity decreased.

[0008]

⁶⁴ Enteral and parenteral nutrition preparations with amino acids as high-quality nitrogen sources have become two important pillars of clinical nutritional support therapy.

⁶⁶ With the continuous deepening and understanding of human and animal metabolism research, the research work of amino acid nutritional preparations is also developing and improving.

⁶⁸ For example, amino acid injections have undergone four generations of product changes so far, from the first generation of protein hydrolyzate; to the second generation of compound crystalline amino acid injections mainly composed of essential amino acids; In recognition of the importance of this topic, the third-generation amino acid injection containing a variety of non-essential amino acids has been developed; in recent years, with the progress of branched-chain amino acid research, the fourth-generation highly branched-chain amino acid injection has been developed.

⁷⁴ However, the composition of commercially available amino acid injections that can be applied clinically has not been perfected so far, and their efficacy in treating critically ill patients is poor. For example, the compound amino acid injection (18AA-II), which is widely used clinically, contains 18 kinds of amino acids and lacks the conditionally essential amino acids glutamine and taurine.

[0009]

⁸¹ Chinese patent 99125545.3 describes the important physiological functions of glutamine and the necessity of supplementation.

⁸³ A technical scheme of an amino acid composition containing L-glutamine or at least one oligomeric peptide of L-glutamine is proposed. In this technical scheme, 16-20 kinds of amino acids are contained, wherein acetylcysteine: acetyltyrosine The amino acid:tryptophan ratio is limited to 0.3-0.8:0.3-0.8:0.9-1.6. The composition of the technical scheme can improve the nitrogen balance of trauma rats, and has remarkable effects on the trauma rats in terms of enhancing immune function, promoting wound healing and proliferation of intestinal mucosal cells.

[0010]

⁹² In the existing theory of amino acid nutrition, whether a slight change in the content of a single amino acid will have a corresponding impact is still a question.

⁹⁴ Surprisingly, however, the inventors discovered by studying the compound composition of amino acids that the ratio of acetylcysteine: acetyltyrosine: tryptophan exceeded 0.3-0.8: 0.3-0.8: 0.9-1.6 and combined with a specific ratio of The new amino acid composition of other amino acids, compared with the existing technical solutions (such as the composition pointed out in Chinese patent 99125545.3), has better nutritional support effects: such as slowing down animal body weight and plasma prealbumin in a state of high catabolic stress It is more effective in the reduction of liver damage and the recovery of liver damage, and it is also better in improving amino acid metabolism disorders and inhibiting catabolism.

[0011]

¹⁰⁴ Contents of the invention

[0012]

¹⁰⁸ Therefore the application provides a kind of compound amino acid composition, comprises the material of following weight ratio:

[0013]

¹¹³ The preferred weight ratio of the above-mentioned composition is:

[0015]

¹¹⁷ The more preferred weight ratio of the above composition is: aspartic acid 4.00, threonine 4.32, serine 5.00, glutamic acid 1.60, proline 5.00, glycine 3.20, alanine 0.60, N(2)-L-propanine Aminoacyl-L-glutamine 18.05, valine 9.50, methionine 3.20, isoleucine 7.50, leucine 13.00, phenylalanine 3.75, lysine acetate 7.05, histidine 2.60, essence Amino acid 8.60, acetylcysteine 1.01, acetyltyrosine 0.92, tryptophan 1.08, taurine 1.00.

[0016]

¹²⁴ Among the components of the composition, aspartic acid, threonine, serine, glutamic acid, proline, glycine, alanine, valine, methionine, isoleucine, leucine, phenylalanine, lysine acetate, histidine, arginine, tryptophan, taurine, acetylcysteine, etc. have been recorded in the second part of the Chinese Pharmacopoeia 2005 edition.

¹²⁸ Acetylcysteine is also known as N-acetyl-L-cysteine, acetyltyrosine is also known as N-acetyl-L-tyrosine, N(2)-L-alanyl-L-glutamine Aminoamide is also known as L-alanyl-L-glutamine or alanyl glutamine.

[0017]

¹³³ According to the theory proposed by the present invention, those skilled in the art can realize the present invention by adjusting the ratio of each component in the preparation within the ratio range given by the present invention by any means in the art, and can add Other excipient components, such as sodium bisulfite, sodium pyrosulfite, EDTA, citric acid and other commonly used excipients acceptable to humans, or sugar sources such as sorbitol, xylitol, and glucose.

[0018]

¹⁴¹ The active ingredients of each substance in the present invention can exist in the form of appropriate pharmaceutically acceptable salts or short peptides, and the weight ratio is calculated based on the conversion of active ingredients.

¹⁴⁴ For example, it exists in the form of hydrochloride and acetate.

¹⁴⁵ Another example is that the active ingredients are glycyl-L-glutamine, L-cystyl-L-glutamine, L-tyrosyl-L-glutamine, L-leucyl-L-glutamine It exists in the form of short peptides such as aminoamide.

[0019]

¹⁵⁰ On the one hand, the composition of the present invention is used in nutritional therapy or nutritional support to improve the nutritional status of patients.

¹⁵² For example, it can be used in trauma, burns, various surgical operations, severe infection, intestinal flora translocation, and amino acid metabolism disorders and hypoproteinemia caused by various reasons to improve the body's immune function and intestinal function.

[0020]

¹⁵⁸ On the other hand, the composition of the present invention is used in the preparation of products for nutritional therapy or nutritional support, including the preparation of nutritional products for enteral and parenteral intake.

¹⁶¹ Nutritional products ingested through the intestinal tract include health food (which may exist in the form of solid, colloid, liquid or solid-liquid mixture, etc.) and pharmaceuticals administered through the intestinal tract.

¹⁶⁴ Medicines for enteral administration include powders, granules, tablets, capsules, etc.; medicines for parenteral administration include injections (such as sterile powder for injection and injection solution, etc.).
¹⁶⁶ The inner packaging of the injection directly contacting the drug can be a bottle, a double-chamber bag, a multi-chamber bag packaging or a multi-layer co-extruded infusion film (bag) that meets the pharmaceutical requirements and other suitable packaging.
¹⁶⁹ When packing with double-chamber bag, multi-chamber bag or multi-layer co-extruded film (bag) for infusion: the components of the composition of the present invention can be placed in the same chamber (layer), or can be placed in different chambers (layers) In; each component of the composition of the present invention may exist partially or completely in the form of solid, and may also be partially or completely dissolved in a suitable solvent such as water.

[0021]

¹⁷⁷ Those skilled in the art can realize the present invention by any means in the field according to the theory proposed by the present invention.

[0022]

¹⁸² The following examples will illustrate the present invention in more detail, but do not limit the present invention.

[0023]

¹⁸⁷ Example

[0024]

¹⁹¹ Comparative Example 1:

[0025]

¹⁹⁵ Compound Amino Acid Injection (18AA-II): Each 1000ml contains 5.00g histidine, 5.00g proline, 8.40g arginine, 4.20g isoleucine, 3.40g serine, 2.50g aspartic acid, leucine Amino acid 5.90g, threonine 4.20g, cystine 0.20g, lysine acetate 9.50g, tryptophan 1.40g, glutamic acid 4.20g, methionine 4.20g, tyrosine 0.20g, glycine 5.90g, phenylalanine 5.90g, valine 5.50g.

[0026]

²⁰² Comparative example 2 (Chinese patent 99125545.3 embodiment 5 formula):

[0027]

²⁰⁶ Under nitrogen protection, aspartic acid 4.0g, threonine 5.4g, serine 5.0g, glutamic acid 1.6g, proline 5.0g, glycine 1.9g, N(2)-L-alanyl-L- Glutamine 18.2g, Valine 9.5g, Methionine 4.3g, Isoleucine 7.5g, Leucine 13.0g, Phenylalanine 3.8g, Lysine 5.0g, Histidine 2.6g , 8.6g of arginine, 0.8g of acetylcysteine, 0.8g of acetyltyrosine, 1.1g of tryptophan, 1.0g of taurine, 0.5g of sodium bisulfite are dissolved in water for injection and adjusted to 1000ml , filtered, filled in a 250ml infusion bottle, stoppered and capped, heat sterilized, and cooled to obtain an injection.

[0028]

²¹⁵ Example 1:

[0029]

²¹⁹ Under nitrogen protection, aspartic acid 4.00g, threonine 4.32g, serine 5.00g, glutamic acid 1.60g, proline 5.00g, glycine 3.20g, alanine 0.60g, N(2)-L- Alanyl-L-glutamine 18.05g, valine 9.50g, methionine 3.20g, isoleucine 7.50g, leucine 13.00g, phenylalanine 3.75g, lysine acetate 7.05 g, histidine 2.60g, arginine 8.60g, acetylcysteine 1.01g, acetyltyrosine 0.92g, tryptophan 1.08g, taurine 1.00g, sodium bisulfite 0.5g in water for injection Dissolve in 1000ml and make up to 1000ml, filter, fill in 250ml infusion bottle, stopper and cover, heat sterilize, cool to get injection.

[0030]

²²⁸ A variety of drug efficacy tests conducted by the inventors show that the present invention has a good nutritional support effect, and is superior to existing technical solutions in many aspects.

²³⁰ With embodiment 1 and comparative example 1 injection through total intravenous nutrition administration to short bowel syndrome rat test, in reflecting some indexes of body immune function (thymus index, peripheral blood T lymphocyte transformation rate and stimulation index , CD4+/CD8+ ratio), the animals in the administration group of Example 1 were significantly higher than the animals in the administration group of Comparative Example 1 (the results are shown in Table 1), showing that the present invention can more obviously improve the immune function of the body.

[0031]

²³⁹

Table 1 Changes in indicators of immune function

[0032]

²⁴³ Compared with Example 1, ★: P<0.05

[0033]

²⁴⁷ The nutritional support effect of the present invention will be described in detail below through the drug effect

test on severely burned Beagle dogs.

[0034]

²⁵² (1) Animal model making and grouping

[0035]

²⁵⁶ It is a British purebred adult Beagle dog, weighing 8.5-10.5Kg, fed in a single cage with a special formula feed, adaptively fed for half a month, and grouped into groups after training and inspection.

[0036]

²⁶¹ British purebred adult Beagle dogs were depilated with 20% sodium sulfide depilatory agent on the back, and calculated according to the cowgiell-Dralking formula to determine the burn area and area of each dog.

²⁶³ After each animal was anesthetized, it was smeared on the test area with 3% napalm, covered with wet cotton cloth around it, and ignited and burned for 50 seconds, causing deep III ° burns on 30% of the body surface area.

²⁶⁶ According to the way of supplementing nutrition for severe burns, the principle of comprehensive treatment is the principle of enteral nutrition as the main and parenteral nutrition as the supplement.

²⁶⁸ Animals are randomly divided into 3 groups according to body weight and sex: Comparative Example 1 group (transfusion and compound amino acid injection (18AA-II)), comparative example 2 groups (transfusion and comparative example 2 injection) and embodiment 1 group (infused with embodiment injection).

²⁷² There were 7 dogs in each group (3 females and 4 males). The energy nitrogen source (217.6KJ) of the injection was input per 10Kg of body weight per day. The enteral nutrition of each group was the same formula feed, and each dog consumed 200g/d.

[0037]

²⁷⁸ (2) Treatment and wound treatment

[0038]

²⁸² Resuscitation: In the first 24 hours of burn injury, each group received the same intravenous fluid infusion with crystal colloid 1:1; in the second 24 hours, the volume of resuscitation was half of that in the first 24 hours. Drink water and eat 1/2 equal amount of constant enteral nutrition freely; resume the same amount of full enteral nutrition diet from the third day, and at the same time intravenously infuse the nutrient supply of each setting group until 21 days.

[0039]

290 After burn, the animal wounds in each group were smeared with 2.5% iodine, 4 times a day. After the wounds were ulcerated, they were washed with saline, and then reapplied with iodine 4 times a day.
292 If the fever persists for 2 consecutive days, intramuscular or intravenous infusion of gentamicin.
293 Burned animals were given debridement every day from the seventh day, depending on the specific situation of the wound, and the burn wound was completely removed by 16 days after injury.

[0040]

298 (3) Data and statistical processing

[0041]

302 The experimental results are expressed as mean ($\bar{x}$) $\pm$ standard deviation (s).
303 Measurement data were compared using Student t test and analysis of variance, and $P < 0.05$ was considered statistically significant.

[0042]

308 (4) Nutritional support evaluation results

[0043]

312 1. Changes in body weight

[0044]

316 From the change data of each group's body weight, it can be seen that Embodiment 1 group is better than Comparative Example 1 group and Comparative Example 2 group to the maintenance of burn Beagle dog body weight effect: after injury, each group's average body weight significantly reduces in 21 days, but Comparative Example 1 Group and comparative example 2 group reduction degree is higher than embodiment 1 group.

[0045]

324 Table 2 Experimental Beagle dog body weight change after burn ($\bar{x} \pm s$)
(Kg)

[0046]

329 Compared with before injury, ★★: $P < 0.01$

[0047]

333 2. Liver function

[0048]

337 The change of plasma ALT concentration in each group of table 3 shows that burn can cause Beagle dog liver to be damaged to some extent in the early stage, and the effect that embodiment 1 group makes liver damage recovery is better than comparative embodiment 1 group and comparative embodiment 2 groups to a certain extent: injury After 7 days, there was no significant difference between the Example 1 group and the pre-injury, while the comparison between the Comparative Example 1 group and the Comparative Example 2 group was still significantly higher than that before the injury ($P < 0.05$).

[0049]

346 Table 3 Changes of plasma ALT after burn in experimental Beagle dogs ($\bar{x} \pm s$)
(μ /L)

[0050]

351 Compared with before injury, ★: $P < 0.05$, ★★: $P < 0.01$

[0051]

355 3. Small intestine function

[0052]

359 Three days after the injury, the plasma D-lactic acid concentration in each group increased in varying degrees, and only the comparison example 2 group had a significant difference ($P < 0.01$), and all the other time points were compared with the example 1 group at 21 days. Except for a significant increase ($P < 0.01$), there was no change in the groups of Comparative Example 2 and Example 1 (Table 4).

363 It shows that treatment with the injection preparation of Comparative Example 1 for a long time may increase the intestinal permeability of burnt Beagle dogs, resulting in the risk of translocation infection of intestinal flora.

366 Compared with Example 2 and Example 1, it is beneficial to maintain the permeability of the intestinal tract during the treatment of burned Beagle dogs and prevent translocation infection of intestinal flora.

[0053]

371 Table 4 Changes of plasma D-lactic acid ($\bar{x} \pm s$) (μ g/ml) after Beagle dogs were burned

[0054]

³⁷⁶ Compared with before injury, ★: P<0.05, ★★: P<0.01

[0055]

³⁸⁰ 4. Changes in nutritional indicators

[0056]

³⁸⁴ Embodiment 1 injection preparation is significantly better than comparative example 1 and comparative example 2 (P<0.05) to the reducing effect of suppressing burn Beagle dog plasma prealbumin (PreA): from 3 days after injury, each group test result Although they were all significantly lower than the respective pre-injury values (P<0.05-0.01), the plasma prealbumin of Example 1 group was significantly higher than that of Comparative Example 1 and Comparative Example 2 groups (P<0.05-0.01) at 14 days and 21 days. 0.01).

[0057]

³⁹² Table 5 Changes of plasma prealbumin (PreA) after experimental Beagle dog burn ($\bar{x} \pm s$) (g/L)

[0058]

³⁹⁷ Compared with before injury, ★: P<0.05, ★★: P<0.01.

³⁹⁸ Compared with Example 1, *: P<0.05, **: P<0.

01

[0059]

⁴⁰⁵ Whole blood hemoglobin, plasma total protein (TP) and plasma albumin (ALB) in each group after injury were significantly decreased and there was no significant difference among the groups.

⁴⁰⁷ But despite this, at 21 days, the reduction range of whole blood hemoglobin in the groups of Comparative Example 2 and Example 1 was 8% less than that of the Group of Comparative Example 1 (Table 6).

[0060]

⁴¹² Table 6 The change of whole blood hemoglobin ($\bar{x} \pm s$) (g/L) after experimental Beagle dog burn

[0061]

⁴¹⁷ Compared with before injury, ★: P<0.05, ★★: P<0.01.

[0062]

⁴²¹ 5. Changes in plasma amino acids

[0063]

⁴²⁵ From the amino acid changes in the plasma of the following groups, it can be seen that the injection preparation of Example 1 is superior to the injection preparations of Comparative Example 1 and Comparative Example 2 for correcting the disorder of amino acid metabolism in Beagle dog plasma after burn.

[0064]

⁴³² 21 days after comparative example 1 group Beagle dog burns, plasma total amino acid content still significantly reduces (P<0.05-0.01), has aspartic acid, serine, glutamine, glycine, alanine, tyrosine, tryptophan Metabolic disorders (decreased/increased content) occurred in 11 kinds of amino acids including lysine, histidine, arginine and proline.

[0065]

⁴³⁹ In comparison example 2, the plasma total amino acid content in group 2 was still significantly reduced (P<0.05-0.01) at post-injury 21 days, and a total of 10 kinds of amino acids had metabolic disorders (decreased/increased content).

[0066]

⁴⁴⁵ The total amino acid content of the dogs in Example 1 group reached the pre-injury level 21 days after the injury; only 4 kinds of amino acids had metabolic disorders (decreased/increased content).

[0067]

⁴⁵⁰ The change ($\bar{x} \pm s$) ($\mu\text{mol/L}$) of plasma amino acid after table 7 comparative embodiment 1 group Beagle dog burns

[0068]

⁴⁵⁵ Compared with before injury, ★: P<0.05, ★★: P<0.01.

[0069]

⁴⁵⁹ The change ($\bar{x} \pm s$) ($\mu\text{ mol/L}$) of plasma amino acid after table 8 contrasts embodiment 2 groups Beagle dog burns

[0070]

⁴⁶⁴ Compared with before injury, ★: $P < 0.05$, ★★: $P < 0.01$.

[0071]

⁴⁶⁸ Changes ($\bar{x} \pm s$) ($\mu\text{ mol/L}$) of plasma amino acids after table 9 embodiment 1 group Beagle dog burns

[0072]

⁴⁷³ Compared with before injury, ★: $P < 0.05$, ★★: $P < 0.01$.

[0073]

⁴⁷⁷ 6. 24-hour urinary urea nitrogen content

[0074]

⁴⁸¹ The experimental results illustrate that the injection preparation of Example 1 is significantly better than the injection preparation of Comparative Example 1 and Comparative Example 2 in inhibiting the catabolism of the burned Beagle dog: the discharge amount of the Comparative Example 1 group is significantly higher than that of Example 1 in 3 days after injury group ($P < 0.05$); 14 days and 21 days after injury, the excretion of Example 2 group was significantly higher than that of Example 1 group ($P < 0.05$).

[0075]

⁴⁸⁹ Table 10 Experimental Beagle dog 24-hour urine urea nitrogen content changes ($\bar{x} \pm s$) (g/L)

[0076]

⁴⁹⁴ Compared with before injury, ★: $P < 0.05$, ★★: $P < 0.01$.

⁴⁹⁵ Compared with Examples, *: $P < 0.05$.

[0077]

⁴⁹⁹ In summary of the above experimental results, compared with Comparative Example 2 and the compound

amino acid injection (18AA-II) that is currently marketed as being considered to have a good nutritional support treatment effect, the composition of the present invention not only slows down the treatment of burns in dogs. It is more effective in reducing body weight and plasma prealbumin and recovering liver damage, and it is also better in improving amino acid metabolism disorders after burns and inhibiting catabolism after burns.

505 In addition, the composition of the present invention is also superior to the compound amino acid injection (18AA-II) in protecting the intestinal barrier function.

507 Thus it is shown that the composition of the present invention has a better nutritional support effect than the prior art scheme.