尿囊素 .Allantoin

Overview:

Allantoin is a natural compound concentrated in comfrey root that promotes wound healing, speeds up cell regeneration and has a skin-softening (keratolytic) effect. The Merck Index lists the therapeutic applications of allantoin as a topical vulnerary (wound healer) and treatment for skin ulcers. The FDA has approved allantoin skin creams (0.5% to 2.0%) as non-prescription drug products for: 1) the temporary protection of minor cuts, scrapes, burns and sunburn; 2) preventing and protecting skin and lips against chapping, chafing, cracking and wind-burn, and 3) relieving dryness and softening cold sores and fever blisters.

Allantoin is also recommended for treating and preventing diaper rash and additionally helps to seal out wetness. Allantoin is also used in shampoos, foam baths, baby powders, lipsticks, various dental preparations and topical pharmaceuticals. The FDA OTC (over-the-counter Drug) Panel does not recognize allantoin as a wound-healing agent, only as a skin protectant. However, allantoin is ter ed as a cell proliferant and epithelization (skin growth) stimulant in texts including the "United States Dispensatory", "Merck Index", and "British Pharmaceutical Codex". Allantoin is said to clean away dead (necrotic) tissue and hasten the growth of new healthy tissue. Since allantoin stimulates new and healthy tissue growth, skin formation may take place over wounds and sores. Allantoin has also been termed a counter irritant that helps alleviate the skin-irritation effects of certain cosmetic ingredients including soaps, detergents, surfactants, oils, and acidic or alkaline materials. Allantoin produces its desirable effects by promoting and speeding up the healthy, natural processes of the body. It is said to help the skin to help itself. Allantoin is the soothing and healing constituent in comfrey root, valued for use in creams and lotions for these properties. Comfrey teas containing allantoin are also recommended for speeding the healing of bruises, sprains, bone fractures and broken bones.

Allantoin is a botanical extract of the comfrey plant and is used for its healing, soothing, and anti-irritating properties. Allantoin helps to heal wounds and skin irritations and stimulate growth of healthy tissue. This

extract can be found in anti-acne products, sun care products, and clarifying lotions because of its ability to help heal minor wounds and promote healthy skin.

Its chemical formula is C4H6N4O3. It is also called 5-ureidohydantoin, glyoxyldiureide, and 5-ureidohydantoin. It is a product of oxidation of uric acid. It is a diureide of glyoxilic acid. It is a product of purine metabolism in most mammals except higher apes, and it is present in their urine.

The keratolytic effect and abrasive and adstringent properties of allantoin are used in skin softening cosmetic preparations. It is also frequently present in toothpaste, mouthwash, and other oral hygiene products, in shampoos, lipsticks, various cosmetic lotions and creams, and other cosmetic and pharmaceutical products.

Chemistry:

Allantoin, in its pure form, is a white, odourless, crystalline powder, soluble in water and alcohol and almost insoluble in ether. The Merck Index describes allantoin as a product of purine metabolism that is industrially prepared synthetically by a process using uric acid. It is nontoxic, nonirritating and non-allergenic. Chemical name: glyoxyl-diureide. Molecular weight: 158.12. Melting range: 225C Heavy metals: 10 ppm maximum. Solubility in water: 0.5% at 25C. Can dissolve in hot water, hot mellow, watery sodium hydroxide solution , dissolve in the water and mellow with normal temperature slightly, hardly dissolve in the organic solvents such as aether and chloroform. Its saturated watery solution (concentration is 0.6 %) presents the slight acidity . PH value is 5.5 , stable in the watery solution with PH value 4—9, also stable in non-watery solvents and dry air , can be seethed in strong alkali solution and decompose by exposing to the sunlight .

SYNONYMS:

5-Ureidohydantoin; Glyoxyldiureide; Alantan; Alloxantin;

Ureidohydantoin; Hemocane; Paxyl; Allantol; Cordianine; Glyoxyldiureid; Hydantoin, 5-ureido-; 2,5-Dioxo-4-imidazolidinyl-urea;

Chemical name

(2,5-Dioxo-4-imidazolidinyl) urea

DESCRIPTION: When isolated, Allantoin is a white, odorless, crystalline powder.	
CHEMICAL NAME:	GLYOXYL-DIUREIDE
INCI ADOPTED NAME:	ALLANTOIN
FDA CLASSIFICATION:	Category I (Safe and Effective) OTC Tentative Final Monograph on Skin Protectant Drugs
MOLECULAR FORMULA:	C4H6N4O3
MOLECULAR WEIGHT:	158.12

Suggested Amount:

Use rate of allantoin is 0.5 – 2.0% w/w. Small concentrations can be added to the water phase, to incorporate more than 0.5% into an emulsion, add during the cooling phase once the temperature has dropped below 50 °C/122°F.

Simultaneous Measurement of Allantoin and Urate in Plasma: Analytical Evaluation and Potential Clinical Application in Oxidant:Antioxidant Balance Studies:

In humans, allantoin is formed by nonenzymatic oxidation of urate; it may, therefore, be useful in assessing oxidative stress. Most published

methods involve separate analysis of urate and allantoin and require extraction, hydrolysis, and derivatization procedures . The primary aim of this study was to evaluate a slightly modified version of an HPLC assay described by Lux et al. for the simultaneous measurement of urate and allantoin. A secondary aim was to explore the clinical utility of allantoin as a biomarker of oxidative stress, the hypothesis being that in disease associated with increased oxidative stress, allantoin increases because of an increased "oxidative turnover" of urate. The final aim of the study was to investigate the effect of age on urate and allantoin concentrations.

Allantoin and uric acid were from Sigma; 1-heptanesulfonic acid, sodium salt monohydrate was from Sigma-Aldrich; potassium dihydrogen phosphate was from Merck; sodium hydroxide was from Riedel-de Haen; orthophosphoric acid was from BDH, and Moni-Trol Level 1 Chemistry Control Serum was from Dade International. MilliQ water (Millipore ultra-pure water system; Millipore) was used for preparation of all solutions. Aqueous stock solutions of allantoin (1000 μmol/L) and urate (2000 μmol/L) were prepared and stored at 4 °C. Because uric acid (urate) is more soluble at alkaline pH, sodium hydroxide (1 mol/L) was added dropwise until the pH was ~9.0; at this pH, all urate was dissolved. Calibrators (10–100 μmol/L for allantoin; 50–1000 μmol/L for urate) were prepared in mobile phase from stock solutions: 25 μL of each calibrator was mixed with 25 μL of Moni-Trol control serum and 75 μL of mobile phase. Ultrafiltrates (see below) of diluted calibrators were used to construct daily calibration curves. For precision studies, we used 1-mL aliquots of pooled heparinized plasma with or without added allantoin (25 μL of stock solution) and urate (250 μL of stock solution) to prepare control samples. For sample preparation, we vortex-mixed 25.0 μL of sample or control with 100 μL of mobile phase, transferred the mixture into a filter unit (Millipore Ultrafree-MC 30 000 NMWL polysulfone-membrane filter unit; Millipore) that had been prewashed twice before use with 300 μL of water to remove the humectant (glycerol), and centrifuged the mixture in a MSE Micro Centaur (MSE Scientific Instruments) at 2500*g* for 10 min to remove protein and other molecules of M_r >30 000. Ultrafiltrate (20 μL) was injected into the HPLC system, which comprised an isocratic pump (ISCO model 2350 pump with a 20-μL looped Valco manual injector; ISCO), a variable wavelength absorbance detector (ISCO model V4 detector with 5-mm flow cell path), a cartridge guard column (Spherisorb C_{18}, 5 μm, 10 x 4.6 mm i.d. cartridge; ISCO), and a reversed-phase analytical column (ISCO C_{18}, 5 μm, 250 x 4.6 mm i.d.). The mobile phase

was aqueous 5 mmol/L potassium dihydrogen phosphate containing 5 mmol/L 1-heptanesulfonic acid (ion-pairing reagent) and adjusted to pH 3.1 using orthophosphoric acid. The flow rate was 1.0 mL/min, and detection was at 210 nm.

Because urate reportedly is less stable at alkaline pH (2), the stability of the stock urate calibrator (pH 9.4) was assessed. To check whether membrane filtration caused loss of analyte, fresh fasting, heparinized plasma was analyzed with and without filtration. Linearity was assessed by repeated measurements of Moni-Trol control at various concentrations. Recovery was assessed by the addition of allantoin (25 μmol/L) and urate (250 μmol/L) to pooled plasma. A signal-to-noise ratio of 3:1 was used to determine detection limits.

This study was approved by the Ethics Subcommittee of the Hong Kong Polytechnic University, and all procedures involving human subjects complied with the Declaration of Helsinki, as revised in 1996.

The method showed clear separation of allantoin and urate, with retention times of 3.0 and 9.5 min, respectively (Fig. 1). The detection limit for allantoin and urate in mobile phase was 20 pmol (equivalent to a plasma concentration of 5 μmol/L). The within- (n = 9) and between-day (n = 6) CVs for allantoin (15-25 μmol/L) were <4% and <7%, respectively; the within- and between-day CVs for urate (50-500 μmol/L) were <4%. The calibration curves were linear to 100 μmol/L for allantoin and 1000 μmol/L for urate. Recovery (n = 6) was 92% for allantoin and 98% for urate. Aqueous allantoin and urate (pH 9.4) stock calibrators were stable at 4 °C for at least 7 and 2 weeks, respectively

Figure 1. Typical chromatograms of allantoin and urate. (A), pure calibrators (allantoin prepared in water, and urate in dilute sodium hydroxide solution) were diluted and mixed in mobile phase. The final mixture was injected directly into the HPLC system without ultrafiltration. (B), fasting heparinized plasma from one healthy subject, after ultrafiltration.

Table 1. Allantoin and urate concentrations in biological fluids, as reported in current and previous studies.

Subjects	n	Sample type	Allantoin, μmol/L: range and/or mean (SD)	Urate, μmol/L: range and/or mean (SD)	Allantoin:urate ratio, %: range and/or mean (SD)	Reference
Healthy adults	40; 23 males, 17 females	Fasting plasma	14.8 – 27.8; 20.8 (3.8) males, 21.0 (2.0) females	241 – 477; 380 (59) males, 290 (41) females	5.55 (1.11) males, 7.37 (1.26) females	Current study
NIDDM patients	64; 27 males, 37 females	Fasting plasma	14.5 – 48.2; 23.7 (6.6) males, 23.0 (6.0) females	135 – 635; 366 (98) males, 352 (112) females	6.77 (2.06) males, 6.87 (1.73) females	Current study
Healthy adults	7; 4 males, 3 females	Fasting plasma	14.1 – 25.4; 18.6 (3.8) all	258 – 621; 432 (121) all	4.7 (1.6) all	Grootveld and Halliwell *(2)*
RA[a] patients	9; 1 male, 8 females	Synovial fluid	7.2 – 31.3; 29.9 (7.3) all	123 – 351; 205 (92) all	11.8 (5.6) all	Grootveld and Halliwell *(2)*
RA patients	4; 2 males, 2 females	Fasting plasma	20.3 – 45.2; 36.1 (6.3) all	273 – 485; 375 (102) all	10.5 (3.8) all	Grootveld and Halliwell *(2)*
Healthy adults	99 males	Plasma	2.4 (0.6)		Approximately 1%	Lagendijk et al. *(3)*
Healthy adults	18 (no M/F information)	Plasma	12.4 – 20.6	270 – 390		Lux et al. *(7)*

Healthy adults	8 males	Plasma	11.9 (2.6)	305 (16)	Hellsten et al. *(5)*
Healthy adults	171 males	Serum	15.7 (7.9)	206 (55) males, 320 (55) females	Kock et al. *(6)*
Healthy adults	15; 9 males, 6 females	Fasting plasma	25	240 – 450; 370 (80) all	Naidoo and Lux *(9)*

TOXICOLOGICAL DATA:

The U.S. Food and Drug Administration (FDA) has classified Allantoin as a Category I (safe and effective) active ingredient skin protectant.

The FDA's Tentative Final Monograph on skin protectant drug products for Over-The-Counter (OTC) human use was published in the Federal Register (Volume 48, No. 32, pp. 6820-33 and Volume 55, No. 11, pp. 25240-81). Based on the wide use and clinical acceptance of Allantoin, as well as published reports in the literature, the FDA has approved the following statements for non-prescription, drug products containing Allantoin at 0.5% to 2.0%.

1. For the temporary protection of minor cuts, scrapes, burns and sunburn.
2. Helps prevent and temporarily protects chafed, chapped, cracked, or wind-burned skin and lips.
3. Relieves dryness and softens cold sores and fever blisters.
4. Helps treat and prevent diaper rash. Protects chafed skin/minor skin irritation due to/associated with diaper rash and helps protect from/seal out wetness.

Allantoin is considered to be nontoxic, nonirritating and non-allergenic by the Schwartz patch test on 200 individuals, as published in the Federal Register (Volume 43, No. 151, pp. 34632-34). Clinical and marketing experience has confirmed that Allantoin is safe and effective in the dosage range recommended (0.5 to 2.0%) as a skin protectant.

Main Purpose：

Allantoin is a kind of important fine chemical with a broad purpose, universally used in pharmaceuticals, light industry, agriculture, daily chemicals and biology engineering.

1.In pharmaceuticals:

Allantoin has many physiologies such as accelerating the growth of the cells, expediting the wound to cicatrize, intenerating horn albumen ,etc and it is also a good cicatrisation and anti-canker dosage for the skin wound which can be used to relax and cure skin xerosis ,dry scaly skin bits, skin canker, alimentary canal canker and inflammation and have a preferable curative effects on the osteomyelitis , diabetes, hepatocirrhosis and acne.