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(54) **METHODS OF THERAPEUTIC MONITORING OF NITROGEN SCAVENGING DRUGS**

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See application file for complete search history.

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(56) **References Cited**

U.S. PATENT DOCUMENTS

4,284,647 A 8/1981 Brusilow et al.
4,457,942 A 7/1984 Brusilow
5,654,333 A 8/1997 Samid
5,968,979 A 10/1999 Brusilow
6,050,510 A 4/2000 Bonnewitz

(Continued)

FOREIGN PATENT DOCUMENTS

WO WO94/22494 10/1994
WO WO 2005/053607 A1 6/2005

(Continued)

OTHER PUBLICATIONS

Batshaw, M.L. et al. (Aug. 1981) "New Approaches to the Diagnosis and Treatment of Inborn Errors of Urea Synthesis," *Pediatrics* 68(2):290-297.

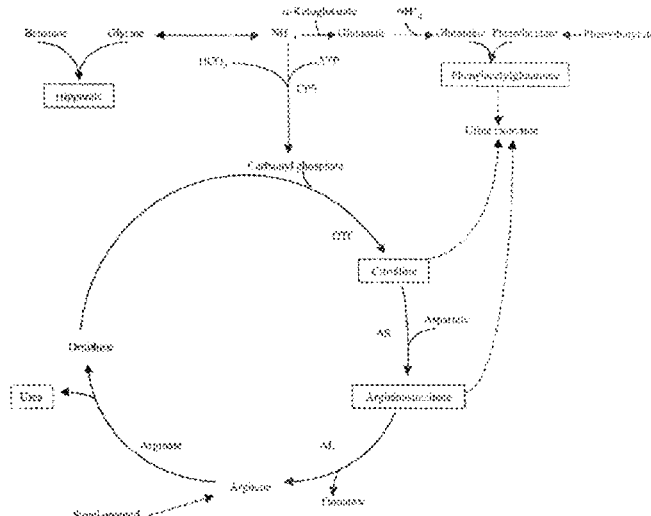
(Continued)

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(57) **ABSTRACT**

The present disclosure provides methods for evaluating daily ammonia exposure based on a single fasting ammonia blood level measurement, as well as methods that utilize this technique to adjust the dosage of a nitrogen scavenging drug, determine whether to administer a nitrogen scavenging drug, and treat nitrogen retention disorders.

15 Claims, 3 Drawing Sheets



(56)

References Cited

U.S. PATENT DOCUMENTS

6,083,984	A	7/2000	Brusilow
6,219,567	B1	4/2001	Eggers
8,094,521	B2	1/2012	Levy
8,404,215	B1	3/2013	Scharschmidt et al.
8,642,012	B2	2/2014	Scharschmidt
2003/0195255	A1	10/2003	Summar
2004/0229948	A1	11/2004	Summar et al.
2005/0273359	A1	12/2005	Young
2006/0135612	A1	6/2006	Ferrante
2008/0119554	A1	5/2008	Jalan et al.
2010/0008859	A1	1/2010	Scharschmidt
2010/0016207	A1	1/2010	Wurtman et al.
2012/0022157	A1	1/2012	Scharschmidt
2012/0220661	A1	8/2012	Lee
2013/0210914	A1	8/2013	Scharschmidt
2013/0281530	A1	10/2013	Scharschmidt et al.
2014/0142186	A1	5/2014	Scharschmidt et al.

FOREIGN PATENT DOCUMENTS

WO	WO 2006/056794	6/2006
WO	WO 2007/005633	1/2007
WO	WO 2009/087474	7/2009
WO	WO 2009/134460	A1 11/2009
WO	WO 2010/025303	A1 3/2010
WO	WO 2012/028620	3/2012
WO	WO2013/048558	4/2013
WO	WO2013/158145	10/2013

OTHER PUBLICATIONS

Brahe, C., et al., (2005) "Phenylbutyrate Increases SMN Gene Expression in Spinal Muscular Atrophy Patients," *Eur J Hum Genet* 13:256-259.

Brunetti-Pierri, N., et al., (2011) "Phenylbutyrate Therapy for Maple Syrup Urine Disease," *Hum Mol Genet* 20(4):631-640.

Chung, Y.L., et al., (2000) "A Novel Approach for Nasopharyngeal Carcinoma Treatment Uses Phenylbutyrate as a Protein Kinase C Modulator: Implications for Radiosensitization and EBV-Targeted Therapy," *Clin Cancer Res* 6:1452-1458.

Cudkovicz, ALS (2009) "Phase 2 Study of Sodium Phenylbutyrate in ALS," *Amyotrophic Lateral Sclerosis* 10:99-106.

Diaz, G.A., et al., "Phase 3 Blinded, Randomized, Crossover Comparison of Sodium Phenylbutyrate (NaPBA) and Glycerol Phenylbutyrate (GPB): Ammonia (NH₃) Control in Adults with Urea Cycle Disorders (UCDs)," *Mol. Genet. Metab.* 102:276, Society of Inherited Metabolic Disease (SMID) Abstract.

Enns, G.M., et al., (2007) "Survival After Treatment with Phenylacetate and Benzoate for Urea-Cycle Disorders," *N. Eng J Med* 356:2282-2292.

Gropman, A. (2010) "Brain Imaging in Urea Cycle Disorders," *Mol Genet Metab* 100:S20-S30.

Hines, P., et al., (2008) "Pulsed-Dosing with Oral Sodium Phenylbutyrate Increases Hemoglobin F in a Patient with Sickle Cell Anemia," *Pediatr Blood Cancer* 50:357-359.

Hogarth, P., et al., (2007) "Sodium Phenylbutyrate in Huntington's Disease: A Dose-Finding Study," *Mov Disord* 22(13):1962-1964.

Huang, H.H., et al., (2012) "Cannabinoid Receptor 2 Agonist Ameliorates Mesenteric Angiogenesis and Portosystemic Collaterals in Cirrhotic Rats," *Hepatology* 56:248-258.

Hyperion Therapeutics "Hyperion Therapeutics Announces Enrollment of First Patient in Phase 1/2 Clinical Trial of GT4P in Patients with Urea Cycle Disorders" Announcement, 1 page (Oct. 23, 2007).

Mercuri, E., et al., (2004) "Pilot Trial of Phenylbutyrate in Spinal Muscular Atrophy," *Neuromuscul Disord* 14:130-135.

Mokhtarani, M., et al., (2012) "Elevated Phenylacetic Acid (PAA) Levels Appear Linked to Neurological Adverse Events in Healthy Adults But Not in Urea Cycle Disorder (UCD) Patients," *Mol Genet Metab* 105:342.

Monteleone, JPR, et al., (2012) "Population pk Analysis of Glycerol Phenylbutyrate (GPB) and Sodium Phenylbutyrate (NaPBA) in Adult and Pediatric Patients with Urea Cycle Disorders," *Mol Genet Metab* 105:343.

Ong, J. P., et al., (2003) "Correlation Between Ammonia Levels and the Severity of Hepatic Encephalopathy," *Am. J. Med.* 114:188-193.

Perrine, S. P., (2008) "Fetal Globin Stimulant Therapies in the Beta-Hemoglobinopathies: Principles and Current Potential," *Pediatr Ann* 37(5):339-346.

Ryu, H., et al., (2005) "Sodium Phenylbutyrate Prolongs Survival and Regulates Expression of Anti-Apoptotic Genes in Transgenic Amyotrophic Lateral Sclerosis Mice," *J Neurochem* 93:1087-1098.

Stauch, et al., (1998) "Oral L-ornithine-L-aspartate therapy of chronic hepatic encephalopathy: results of a placebo-controlled double-blind study" *J Hepatology* 28(5):856-864.

Xie, G., et al., (2012) "Role of Differentiation of Liver Sinusoidal Endothelial Cells in Progression and Regression of Hepatic Fibrosis in Rats," *Gastroenterology* 142:S918.

European Patent Office, Extended European Search Report for EP09739263 completed Nov. 2, 2011.

European Patent Office, International Search Report and Written Opinion for PCT/US2009/055256 completed Dec. 18, 2009 and mailed Dec. 30, 2009.

Examination Report for British Patent Application No. GB1013468.2 dated Oct. 28, 2011.

International Preliminary Report on Patentability (Ch I) for PCT/US2012/028620 completed Jun. 4, 2012 and mailed on Apr. 10, 2014.

International Preliminary Report on Patentability (Ch II) for PCT/US2012/028620, completed Aug. 22, 2013 and mailed Sep. 4, 2013.

United States Patent and Trademark Office, International Search Report and Written Opinion for PCT/US2009/030362 mailed Mar. 2, 2009.

United States Patent and Trademark Office, International Search Report and Written Opinion for PCT/US2012/028620 mailed Jun. 20, 2012.

United States Patent and Trademark Office, International Search Report and Written Opinion for PCT/US2012/54673 mailed Nov. 20, 2012.

United States Patent and Trademark Office, International Search Report and Written Opinion for PCT/US2013/71333 mailed Mar. 28, 2014.

Ambrose, A.M. et al. (1933). "Further Studies on the Detoxification of Phenylacetic Acid," *J. Bio. Chem.* 101:669-675.

Batshaw, M.L. et al. (Dec. 1980). "Treatment of Hyperammonemic Coma Caused by Inborn Errors of Urea Synthesis," *J. Pediatr.* 97(6):893-900.

Batshaw, M.L. et al. (Aug. 1981). "New Approaches to the Diagnosis and Treatment of Inborn Errors of Urea Synthesis," *Pediatrics* 68(2):290-297.

Batshaw M.L. et al. (Jun. 10, 1982). "Treatment of Inborn Errors of Urea Synthesis: Activation of Alternative Pathways of Waste Nitrogen Synthesis and Excretion," *N. Engl. J. Med.* 306(23):1387-1392.

Batshaw, M.L. (1984). "Hyperammonemia," in *Current Problems in Pediatrics*, Lockhart, J.D. ed.: Year Book Medical Publishers, pp. 2-69.

Berry, G. T., et al., "Long-Term Management of Patients with Urea Cycle Disorders," *J. Pediatrics* (2001) 138:S56-S61.

Brusilow, S., et al., "Amino Acid Acylation: A Mechanism of Nitrogen Excretion in Inborn Errors of Urea Synthesis," *Science* 207:659-661 (1980).

Brusilow, S. W., et al., "Phenylacetylglutamine May Replace Urea as a Vehicle for Waste Nitrogen Excretion," *Pediatr. Res.* 29:147-150 (1991).

Brusilow, S.w. et al. (Sep. 1, 1979). "New Pathways of Nitrogen Excretion in Inborn Errors of Urea Synthesis," *Lancet* 2(8140):452-454.

Brusilow, S.w. (Jun. 21, 1984). "Treatment of Episodic Hyperammonemia in Children With Inborn Errors of Urea Synthesis," *N. Engl. J. Med.* 310(25):1630-1634.

Brusilow, S.w. (Amendment Dated Jul. 25, 1994). "Protocols for Management of Intercurrent Hyperammonemia in Patients with Urea

(56)

References Cited

OTHER PUBLICATIONS

- Brusilow, S.W. et al. (1991). "Treatment of Urea Cycle Disorders," Chapter 5 in *Treatment of Genetic Diseases*, Desnik, R.J. et al. eds, Churchill Livingstone, New York, New York, pp. 79-94.
- Brusilow, S.W. et al. (1995). "Urea Cycle Enzymes," Chapter 32 in *The Metabolic and Molecular bases of Inherited Diseases*, Scriver, C.R. et al. eds., McGraw-Hill, Inc. New York, New York, pp. 1187-1232.
- Brusilow, S.W., et al. (1996). "Urea Cycle Disorders: Diagnosis, Pathophysiology, and Therapy," *Adv. Pediatr.* 43:127-170.
- Brusilow, S.W., et al. (1995). "Urea Cycle Disorders: Clinical Paradigm of Hyperammonemic Encephalopathy," *Progress in Liver Diseases* (1995) 12:293-309.
- Brusilow, S. W., et al., "Restoration of Nitrogen Homeostasis in a Man with Ornithine Transcarbamylase Deficiency," *J. Metabolism* (1993) 42:1336-1339.
- Calloway, D.H. et al. (1971). "Sweat and Miscellaneous Nitrogen Losses in Human Balance Studies," *J. Nutrition* 101:775-786.
- Calloway, D.H. et al. (1971). "Variation in Endogenous Nitrogen Excretion and Dietary Nitrogen Utilization as Determinants of Human Protein Requirements," *J. Nutrition* 101:205-216.
- Camacho, L.H. et al. (2007, e-pub. Oct. 20, 2006). "Phase I Dose Escalation Clinical Trial of Phenyl butyrate Sodium Administered Twice Daily to Patients With Advanced Solid Tumors," *Invest. New Drugs* 25:131-138.
- Chang J.-G., et al., "Treatment of Spinal Muscular Atrophy by Sodium Butyrate," *PNAS USA* (2001) 98(17):9808-9813.
- ClinicalTrials.gov/Archive View of NCT00551200 on Dec. 11, 2007 "Dose-Escalation Safety Study of Glyceryl Tri (4-Phenylbutyrate)(GT4P) to Treat Urea Cycle Disorders" [accessed Oct. 5, 2009], 4 pages.
- Combined Search and Examination Report mailed on Sep. 9, 2010, for Great Britain Patent Application No. 1013468.2, filed on Aug. 27, 2009, six pages.
- Combined Search and Examination Report mailed on Oct. 9, 2009, for Great Britain Patent Application No. GB0915545.8, filed on Aug. 27, 2009, eight pages.
- Comte, B., et al., "Identification of Phenylbutyrylglutamine, A new Metabolite of Phenylbutyrate Metabolism in Humans," *Journal of Mass Spectrometry* (2002) 37(6):581-590.
- Deferrari, G. et al. (1981). "Brain Metabolism of Amino Acids and Ammonia in Patients with Chronic Renal Insufficiency," *Kidney International* 20:505-510.
- Diaz, G.A., et al., "Phase 3 Blinded, Randomized, Crossover Comparison of Sodium Phenylbutyrate (NaPBA) and Glycerol Phenylbutyrate (GPB): Ammonia (NH₃) Control in Adults with Urea Cycle Disorders (UCDs)," *Mol. Genet. Metab.* 102:276 (2011).
- Examination Report mailed on Oct. 27, 2010, for United Kingdom Patent Application No. GB0915545.8, filed on Aug. 27, 2009, two pages.
- Examination Report mailed Feb. 5, 2010, for United Kingdom Patent Application No. GB0915545.8, filed on Aug. 27, 2009, two page.
- Examination Report mailed May 11, 2010, for United Kingdom Patent Application No. GB0915545.8, filed on Aug. 27, 2009, one page.
- FDA. (Aug. 2003). "Buphenyl® (Sodium Phenylbutyrate) Label" nine pages.
- FDA Label for Buphenyl, 6 pages.
- Gargosky, S. (2006). "High Ammonia Levels Are Associated With Increased Mortality and Coma," *Ucyclyd Pharma, Inc.*, one page.
- Gargosky, S. et al. (Oct. 14, 2005). "Results of a Twenty-two Year Clinical Trial: Actue, Adjunctive Pharmacological Treatment of Hyperammonemic Episodes in Patients with Deficiencies in Enzymes of the Urea Cycle," poster, *Ucyclyd Pharma, Inc.*, one page.
- Gargosky, S. (Aug. 2, 2005). "Improved Survival of Neonates Following Administration of Ammonul® (Sodium Phenyl acetate & Sodium Benzoate) 10% 110% Injection," *SSIEM Poster*, six pages.
- Gharbril, M., et al., "Glycerol Phenylbutyrate (GPB) Administration Gropman, A. L., et al., "1H MRS Allows Brain Phenotype Differentiation in Sisters with Late Onset Ornithine Transcarbamylase Deficiency (OTCD) and Discordant Clinical Presentations," *Mol. Genet. Metab.* 94(1):52-60 (2008).
- Gropman, A.L., et al., "1H MRS Identifies Symptomatic and Asymptomatic Subjects with Partial Ornithine Transcarbamylase Deficiency," *Mol. Genet. Metab.* 95:21-30 (2008).
- Hyperion Therapeutics. (Mar. 30, 2009). "Hyperion Therapeutics Announces Results for Phase II Study in Urea Cycle Disorders," located at <<http://www.hyperiontx.com/press/release/pr1238518388>>, last visited on Apr. 27, 2011, three pages.
- Hyperion Therapeutics. (Jun. 2, 2009). "Hyperion Therapeutics Announces Results of Phase I Study in Patients with Liver Cirrhosis" located at <<http://www.hyperiontx.com/press/release/pr1243891161>>, last visited on Apr. 27, 2011, three pages.
- International Preliminary Report on Patentability mailed on Mar. 1, 2011, for PCT Application No. PCT/US2009/030362, filed on Jan. 7, 2009, seven pages.
- International Preliminary Report on Patentability mailed on Mar. 1, 2011, for PCT Application No. PCT/US2009/055256, filed on Aug. 27, 2009, six pages.
- James, M.O. et al. (1972). "The Conjugation of Phenylacetic Acid in Man, Sub-Human Primates and Some Other Non-Primates Species," *Proc. R. Soc. London* 182:25-35.
- John, BA et al. (Mar. 2009). "The Disposition of HPN-100, A Novel Pharmaceutical Under Development for Potential Treatment of Hyperammonemia, in Cynomolgus Monkeys," abstract presented at ACMG 2009, one page.
- John, BA et al. (Mar. 2009). "The Disposition of HPN-100, A Novel Pharmaceutical Under Development for Potential Treatment of Hyperammonemia, in Cynomolgus Monkeys," ACMG 2009 ADME, poster, two pages.
- Kasumov, T., et al., "New Secondary Metabolites of Phenylbutyrate in Humans and Rats," *Drug Metabolism and Disposition* (2004) 32(1):10-19.
- Lee, B. et al. (Aug. 2009). "Dosing and Therapeutic Monitoring of Ammonia Scavenging Drugs and Urinary Phenylacetylglutamine (PAGN) as a Biomarker; Lessons From a Phase 2 Comparison of a Novel Ammonia Scavenging Agent With Sodium Phenylbutyrate (NaPBA)," abstract presented at ICIEM 2009, San Diego, CA, one page.
- Lee, B. et al. (Aug. 2009). "Dosing and Therapeutic Monitoring of Ammonia Scavenging Drugs and Urinary Phenylacetylglutamine (PAGN) as a Biomarker; Lessons From a Phase 2 Comparison of a Novel Ammonia Scavenging Agent with Sodium Phenyl butyrate (NAPBA)," presented at ICIEM 2009, San Diego, CA, poster, one page.
- Lee, B. et al. (Mar. 2009). "Phase 2 Study of a Novel Ammonia Scavenging Agent in Adults With Urea Cycle Disorders (UCDs)," abstract presented at ACMG 2009, one page.
- Lee, B. et al. (Mar. 2009). "Phase 2 Study of a Novel Ammonia Scavenging Agent in Adults with Urea Cycle Disorders (UCDs)," presented at ACMG 2009, seventeen pages.
- Lee, B. et al. (Aug. 2008). "Preliminary Data on Adult Patients with Urea Cycle Disorders (UCD) in an Open-Label, Switch-Over, Dose-Escalation Study Comparing a New Ammonia Scavenger, Glyceryl Tri (4-Phenylbutyrate) [HPN-100], to Buphenyl® (Sodium Phenylbutyrate [PBAj]," abstract presented at SSIEM 2008, Lisbon, Portugal, one page.
- Lee, B. et al. (Sep. 2008). "Preliminary Data on Adult Patients with Urea Cycle Disorders (UCD) in an Open-Label, Switch-Over, Dose Escalation Study Comparing a New Ammonia Scavenger, Glyceryl Tri (4-Phenylbutyrate) [HPN-100], to Buphenyl® (Sodium Phenylbutyrate [PBA]," presented at SSIEM 2008, Lisbon, Portugal, Poster, one page.
- Lee, B., et al., "Phase 2 Comparison of a Novel Ammonia Scavenging Agent with Sodium Phenylbutyrate in Patients with Urea Cycle Disorders: Safety, Pharmacokinetics and Ammonia Control," *Mol. Genet. Metab.* 100:221-228 (2010).
- Lee, B., et al., "Preliminary Data on Adult Patients with Urea Cycle

(56)

References Cited

OTHER PUBLICATIONS

- Phenylbutyrate (HPN-100), to Buphenyl (Sodium Phenylbutyrate (PBA)),” *J. Inherit. Metab. Dis.* 31(Suppl. 1):91 (2008).
- Lewis, H.B. (1914). “Studies in the Synthesis of Hippuric Acid in the Animal Organism. II. The Synthesis and Rate of Elimination of Hippuric Acid After Benzoate Ingestion in Man,” *J. Bioi. Chem.* 18 :225-231.
- Liang, K.Y., et al., “Longitudinal Data Analysis Using Generalized Linear Models,” *Biometrika* 73(1):13-22 (1986).
- Lichter-Konecki, U., et al., “Ammonia Control in Children with Urea Cycle Disorders (UCDs); Phase 2 Comparison of Sodium Phenylbutyrate and Glycerol Phenylbutyrate,” *Mol. Genet. Metab.* 103:323-329 (2011).
- MacArthur, R. B., et al., “Pharmacokinetics of Sodium Phenylacetate and Sodium Benzoate Following Intravenous Administration as Both a Bolus and Continuous Infusion to Healthy Adult Volunteers,” *Mol. Genet. Metab.* 81:S67-S73 (2004).
- Mansour, A. et al. (Oct. 1997). “Abdominal Operations in Patients with Cirrhosis: Still a Major Surgical Challenge,” *Surqerv* 122(4):730-735. (Abstract Only).
- Masetri, N.E. et al. (Aug. 1992). “Plasma Glutamine Concentration: A Guide in the Management of Urea Cycle Disorders,” *J. Pediatr.* 121 (2):259-261.
- McGuire, B. M., et al., “Pharmacology and Safety of Glycerol Phenylbutyrate in Healthy Adults and Adults with Cirrhosis,” *Hepatology* 51:2077-2085 (2010).
- McGuire, B.M. et al. (2009). “Pharmacokinetic (PK) and Safety Analyses of a Novel Ammonia-Reducing Agent in Healthy Adults and Patients with Cirrhosis,” Hyperion Therapeutics, poster, one page.
- McGuire, B.M. et al. (May 2009). “Pharmacokinetic (PK) and Safety Analyses of a Novel Ammonia-Reducing Agent in Healthy Adults and Patients with Cirrhosis,” abstract presented at DDW, May 2009, two pages.
- McGuire, B. et al. (Apr. 2008). Pharmacokinetic Safety Study of Sodium Phenylacetate and Sodium Benzoate Administered to Subjects With Hepatic Impairments, *Liver International* 28:743. (Abstract Only).
- McGuire, B. et al. (Apr. 2008). “Pharmacokinetic (PK) Safety Study of Sodium Phenylacetate and Sodium Benzoate Administered to Subjects with Hepatic Impairment,” abstract of The 13th International Symposium, Abano (Padova), Italy, Apr. 28-May 1, 2008, two pages.
- McQuade P.S. (1984). “Analysis and the Effects of Some Drugs on the Metabolism of Phenylethylamine and Phenylacetic Acid,” *Neuropsychopharmacol. Bioi. Psychiat.* 8:607-614.
- Piscitelli, S.C. et al. (1995). “Disposition of Phenyl butyrate and its Metabolites, Phenylacetate and Phenylacetylglutamine,” *J. Clin. Pharmacol.* 35:368-373.
- Propst, A. et al. (Aug. 1995). “Prognosis and Life Expectancy in Chronic Liver Disease,” *Dig Dis Sci* 40(8):1805-1815. (Abstract Only).
- Riley, T.R. et al. (Nov. 15, 2001). “Preventive Strategies in Chronic Liver Disease: Part II. Cirrhosis,” *Am. Fam. Physician* 64(10):1735-1740. (Abstract Only).
- Rudman, D., et al., “Maximal Rates of Excretion and Synthesis of Urea in Normal and Cirrhotic Subjects,” *J. Clin. Invest.* (1973) 52:2241-2249.
- Shiple, G.J. et al. (1922). “Synthesis of Amino Acids in Animal Organisms. I. Synthesis of Glycocoll and Glutamine in the Human Organism,” *J. Am. Chem. Soc.* 44:618-624.
- Simell, O., et al., “Waste Nitrogen Excretion Via Amino Acid Acylation: Benzoate and Phenylacetate in Lysinuric Protein Intolerance,” *Pediatr. Res.* 20(11):1117-1121 (1986).
- Singh, “Consensus Statement from a Conference for the Management of Patients with Urea Cycle Disorders,” *Suppl. to J. Pediatrics* (2001) 138(1):S1-S5.
- Summar, M.L. et al. (Oct. 2008, e-pub. Jul. 17, 2008). “Diagnosis, Symptoms, Frequency and Mortality of 260 Patients with Urea Cycle
- Summar, M. et al. (2007). “Description and Outcomes of 316 Urea Cycle Patients From a 21-Year, Multicenter Study of Acute Hyperammonemic Episodes,” Abstract, presented at Annual Symposium CCH—Congress Centre Hamburg, Sep. 4-7, 2007, GSSIEM 2007, two pages.
- Swedish Orphan International. (Jan. 12, 2007). “Urea Cycle Disorders an International Perspective,” Poster, Symposium Swedish Orphan International, Barcelona, Spain, Jan. 12, 2007, one page.
- Tanner, L. M., et al., “Nutrient Intake in Lysinuric Protein Intolerance,” *J. Inherit. Metab. Dis.* 30:716-721 (2007).
- Thibault, A., et al., “A Phase I and Pharmacokinetic Study of Intravenous Phenylacetate in Patients with Cancer,” *Cancer Res.* 54:1690-1694 (1994).
- Thibault, A., et al., “Phase I Study of Phenylacetate Administered Twice Daily to Patients with Cancer,” *Cancer* 75:2932-2938 (1995).
- Tuchman, M. et al. (2008, e-pub. Jun. 17, 2008). “Cross-Sectional Multicenter Study of Patients With Urea Cycle Disorders in the United States,” *Molec. Genetics Metab.* 94:397-402.
- Waterlow, J.C. (Mar. 1963). “The Partition of Nitrogen in the Urine of Malnourished Jamaican Infants,” *Am. J. of Clin. Nutrition* 12:235-240.
- Zeitlin, P.L. et al. (Jul. 2002). “Evidence of CFTR Function in Cystic Fibrosis After System Administration of 4-Phenylbutyrate,” *Mol. Therapy* 6(1):119-126.
- Amodio, P., et al., “Detection of Minimal Hepatic Encephalopathy: Normalization and Optimization of the Psychometric Hepatic Encephalopathy Score. A Neuropsychological and Quantified EEG Study,” *J. Hepatology* 49:346-353 (2008).
- ANDA Notice Letter, Par Pharmaceutical, Inc. to Hyperion Therapeutics, inc.. Re: Glycerol Phenylbutyrate 1.1 gm/ml oral liquid; U.S. Pat. No. 8,404,215 and U.S. Pat. No. 8,642,012 Notice of Paragraph IV Certification Mar. 12, 2014.
- Bajaj, J. S., et al., “Review Article: The Design of Clinical Trials in Hepatic Encephalopathy—An International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) Consensus Statement,” *Aliment Pharmacol Ther.* 33 (7):739-747 (2011).
- Barsotti, Measurement of Ammonia in Blood, 138 *J. Pediatrics*, S11-S20 (2001).
- Batshaw, et al., Treatment of Carbamyl Phosphate Synthetase Deficiency with Keto Analogues of Essential Amino Acids, 292 *The New England J. Medicine*, 1085-1090 (1975).
- Batshaw, M. L. et al., Alternative Pathway Therapy for Urea Cycle Disorder: Twenty Years Later, 138 *J. Pediatrics* S46 (2001).
- Blau, Duran, Blaskovics, Gibson (editors), *Physician’s Guide to the Laboratory Diagnosis of Metabolic Diseases*, 261-276 (2d ed. 1996).
- Blei, A. T., et al., “Hepatic Encephalopathy,” *Am. J. Gastroenterol.* 96(7):1968-1976 (2001).
- Burlina, A.B. et al., Long-Term Treatment with Sodium Phenylbutyrate in Ornithine Transcarbamylase-Deficient Patients, 72 *Molecular Genetics and Metabolism* 351-355 (2001).
- Carducci, M., Phenylbutyrate Induces Apoptosis in Human Prostate Cancer and Is More Potent Than Phenylacetate, 2 *Clinical Cancer Research* 379 (1996).
- Carducci, M.A. et al., A Phase I Clinical and Pharmacological Evaluation of Sodium Phenylbutyrate on a 120-h Infusion Schedule, 7 *Clin. Cancer Res.* 3047 (2001).
- Center for Drug Evaluation and Research, Clinical Pharmacology and Biopharmaceutics Review for New Drug Application No. 20-645 (Ammonul®) (2005).
- Center for Drug Evaluation and Research, Labeling for New Drug Application No. 20-645 (Ammonul®) (2005).
- Center for Drug Evaluation and Research, Medical Review for New Drug Application No. 20-645 (Ammonul®) (2005).
- Chen, Z. et al., Tributyrin: A Prodrug of Butyric Acid for Potential Clinical Application in Differentiation Therapy, 54 *Cancer Research* 3494 (1994).
- Clay, A. et al, Hyperammonemia in the ICU, 132 *Chest* 1368 (2007).
- Collins, A.F. et al., Oral Sodium Phenylbutyrate Therapy in

(56)

References Cited

OTHER PUBLICATIONS

- Conn, H. O., et al., "Liver Physiology and Disease: Comparison of Lactulose and Neomycin in the Treatment of Chronic Portal-Systemic Encephalopathy. A Double Blind Controlled Trial," *Gastroenterology* 72(4):573-583 (1977).
- Cordoba, J., "New Assessment of Hepatic Encephalopathy," *Journal of Hepatology* 54: 1030-1040 (2011).
- Darmaun, D. et al., Phenylbutyrate-Induced Glutamine Depletion in Humans: Effect on Leucine Metabolism, *5 Am. J. of Physiology: Endocrinology and Metabolism* E801 (1998).
- Diaz, G. A., et al., "Ammonia Control and Neurocognitive Outcome Among Urea Cycle Disorder Patients Treated with Glycerol Phenylbutyrate," *Hepatology* 57(6):2171-2179 (2013).
- Dixon, M. A. and Leonard, J.V., Intercurrent Illness in Inborn Errors of Intermediary Metabolism, *67 Archives of Disease in Childhood* 1387 (1992).
- Dover, G. et al, Induction of Fetal Hemoglobin Production in Subjects with Sickle Cell Anemia by Oral Sodium Phenylbutyrate, *54 Cancer Research* 3494 (1994).
- Endo, F. et al., Clinical Manifestations of Inborn Errors of the Urea Cycle and Related Metabolic Disorders During Childhood, *134 J. Nutrition* 1605S (2004).
- European Medicines Agency, Annex I: Summary of Product Characteristics for Ammonaps.
- European Medicines Agency, European Public Assessment Report: Summary for the Public for Ammonaps (2009).
- European Medicines Agency, Scientific Discussion for Ammonaps (2005).
- European Medicines Agency, Scientific Discussion for Carbaglu (2004).
- FDA Label for Carbaglu, seven pages. (Mar. 2010).
- Feillet, F. and Leonard, J.V., Alternative Pathway Therapy for Urea Cycle Disorders, *21 J. Inher. Metab. Dis.* 101-111 (1998).
- Feoli-Fonseca, M. L., Sodium Benzoate Therapy in Children with Inborn Errors of Urea Synthesis: Effect on Carnitine Metabolism and Ammonia Nitrogen Removal, *57 Biochemical and Molecular Medicine* 31 (1996).
- Ferenci, P., et al., "Hepatic Encephalopathy—Definition, Nomenclature, Diagnosis, and Quantification: Final Report of the Working Party at the 11th World Congresses of Gastroenterology, Vienna, 1998," *Hepatology* 35:716-721 (2002).
- Fernandes, Saudubray, Berghé (editors), *Inborn Metabolic Diseases Diagnosis and Treatment*, 219-222 (3d ed. 2000).
- Geraghty, M.T. and Brusilow, S.W., Disorders of the Urea Cycle, in *Liver Disease in Children* 827 (F.J. Suchy et al., eds. 2001).
- Ghabril, M. et al., "Glycerol Phenylbutyrate in Patients with Cirrhosis and Episodic Hepatic Encephalopathy: A Pilot Study of Safety and Effect on Venous Ammonia Concentration," *Clinical Pharmacology in Drug Development* 2(3): 278-284 (2013).
- Gilbert, J. et al., A Phase I Dose Escalation and Bioavailability Study of Oral Sodium Phenylbutyrate in Patients with Refractory Solid Tumor Malignancies, *7 Clin. Cancer Research* 2292-2300 (2001).
- Gore, S. et al., Impact of the Putative Differentiating Agent Sodium Phenylbutyrate on Myelodysplastic Syndromes and Acute Myeloid Leukemia, *7 Clin. Cancer Res.* 2330 (2001).
- Gropman, A.L. et al., Neurological Implications of Urea Cycle Disorders, *30 J. Inher. Metab. Dis.* 865 (2007).
- Hassanein, T. I., et al., "Randomized Controlled Study of Extracorporeal Albumin Dialysis for Hepatic Encephalopathy in Advanced Cirrhosis," *Hepatology* 46:1853-1862 (2007).
- Hassanein, T. I., et al., "Introduction to the Hepatic Encephalopathy Scoring Algorithm (HESA)," *Dig. Dis. Sci.* 53:529-538 (2008).
- Hassanein, T., et al., "Performance of the Hepatic Encephalopathy Scoring Algorithm in a Clinical Trial of Patients With Cirrhosis and Severe Hepatic Encephalopathy," *Am. J. Gastroenterol.* 104:1392-1400 (2009).
- Honda, S. et al., Successful Treatment of Severe Hyperammonemia International Search Report and Written Opinion for PCT/US09/30362, mailed Mar. 2, 2009, 8 pages.
- International Search Report and Written Opinion for PCT/US2009/055256, mailed Dec. 30, 2009, 13 pages.
- Kleppe, S. et al., Urea Cycle Disorders, 5 Current Treatment Options in Neurology 309-319 (2003).
- Kubota, K. and Ishizaki, T., Dose-Dependent Pharmacokinetics of Benzoic Acid Following Oral Administration of Sodium Benzoate to Humans, *41 Eur. J. Clin. Pharmacol.* 363 (1991).
- Lee, B. and Goss, J., Long-Term Correction of Urea Cycle Disorders, *138 J. Pediatrics* S62 (2001).
- Lee, B. et al., Considerations in the Difficult-to-Manage Urea Cycle Disorder Patient, *21 Crit. Care Clin.* S19 (2005).
- Lee, B., et al., "Optimizing Ammonia (NH₃) Control in Urea Cycle Disorder (UCD) Patients: A Predictive Model," Oral Abstract Platform Presentations, Biochemical Genetics, Phoenix, AZ, Mar. 22, 2013.
- Leonard, J.V., Urea Cycle Disorders, *7 Semin. Neonatol.* 27 (2002).
- Lizardi-Cervera, J. et al., Hepatic Encephalopathy: A Review, *2 Annals of Hepatology* 122-120 (2003).
- Maestri NE, et al., Prospective treatment of urea cycle disorders. *J Paediatr* 1991;119:923-928.
- Maestri, N.E., et al., Long-Term Survival of Patients with Argininosuccinate Synthetase Deficiency, *127 J. Pediatrics* 929 (1993).
- Maestri, N.E., Long-Term Treatment of Girls with Ornithine Transcarbamylase Deficiency, *355 N. Engl. J. Med.* 855 (1996).
- Majeed, K., Hyperammonemia, eMedicine.com (Dec. 2001).
- Marini, J.C. et al., Phenylbutyrate Improves Nitrogen Disposal via an Alternative Pathway without Eliciting an Increase in Protein Breakdown and Catabolism in Control and Ornithine Transcarbamylase-Deficient Patients, *93 Am. J. Clin. Nutr.* 1248 (2011).
- Matsuda, I., Hyperammonemia in Pediatric Clinics: A Review of Ornithine Transcarbamylase Deficiency (OTCD) Based on our Case Studies, *47 JMAJ* 160 (2004).
- McGuire, B.M. et al., Pharmacokinetic (PK) and Safety Analyses of a Novel Ammonia-Reducing Agent in Healthy Adults and Patients with Cirrhosis, Hyperion Therapeutics, poster, one page (2009).
- Mizutani, N. et al., Hyperargininemia: Clinical Course and Treatment with Sodium Benzoate and Phenylacetic Acid, *5 Brain and Development* 555 (1983).
- Mokhtarani, M., et al., (2013) "Elevated Phenylacetic Acid Levels Do Not Correlate with Adverse Events in Patients with Urea Cycle Disorders or Hepatic Encephalopathy and Can Be Predicted Based on the Plasma PAA to PAGN Ratio," *Mol Genet Metab* 110(4):446-453.
- Mokhtarani, M., et al., (2012) "Urinary Phenylacetylglutamine as Dosing Biomarker for Patients with Urea Cycle Disorders," *Mol Genet Metab* 107(3):308-314.
- Monteleone, JPR, et al., (2013) "Population Pharmacokinetic Modeling and Dosing Simulations of Nitrogen-Scavenging Compounds: Disposition of Glycerol Phenylbutyrate and Sodium Phenylbutyrate in Adult and Pediatric Patients with Urea Cycle Disorders," *J. Clin. Pharmacol.* 53(7): 699-710.
- Munoz, S. J., "Hepatic Encephalopathy," *Med. Clin. N. Am.* 92:795-812 (2008).
- Nassogne, M.C., Urea Cycle Defects: Management and Outcome, *28 J. Inher. Metab. Dis.* 407 (2005).
- New England Consortium of Metabolic Programs, Acute Illness Protocol: Urea Cycle Disorders: The Infant/Child with Argininosuccinate Lyase Deficiency, adapted from Summar, M and Tuchman, M, Proceedings of a Consensus Conference for the Management of Patients with Urea Cycle Disorders, *138 J. Peds. Suppl.* S6 (2001).
- New England Consortium of Metabolic Programs, Acute Illness Protocol: Urea Cycle Disorders: The Infant/Child with Citrullinemia, adapted from Summar, M and Tuchman, M, Proceedings of a Consensus Conference for the Management of Patients with Urea Cycle Disorders, *138 J. Peds. Suppl.* S6 (2001).
- Newmark, H. L. and Young, W. C., Butyrate and Phenylacetate as Differentiating Agents: Practical Problems and Opportunities, *22 J. Cellular Biochemistry* 247 (1995).

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