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(54) **THERAPY FOR HERPES NEUROLOGICAL VIRAL CONDITIONS UTILIZING 1,4-DIHYDROPYRIDINE CALCIUM CHANNEL BLOCKERS**

(76) Inventor: **Howard M. Zik**, 3169 Gomer St., Yorktown Heights, NY (US) 10598

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(58) **Field of Search** **514/356, 262**

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Primary Examiner—William R. A. Jarvis

(74) *Attorney, Agent, or Firm*—Gottlieb, Rackman & Reisman, P.C.

(57)

ABSTRACT

A therapy for Bells Palsy in mammals is proposed that rests on a causal hypothesis involving both endothelin and the herpes virus, particularly the herpes simplex virus for Bell's Palsy. Similarly, the same therapy would apply to Ramsay Hunt, but in this case the herpes zoster virus would be involved in the causal hypothesis. Other herpes viral related conditions are also suggested to be amenable such as herpes simplex encephalitis. The therapy uses therapeutically effective doses of calcium channel blockers that are of the 1,4-dihydropyridine derivative class, such as felodipine but also including nifedidine, nimodipine, nisodipine or alendipine. The treatment is proposed as continuing up to the tenth day of progression, but to be started as early as possible. Acyclovir or other herpes antagonists such as famciclovir may also be administered in therapeutically effective dosages.

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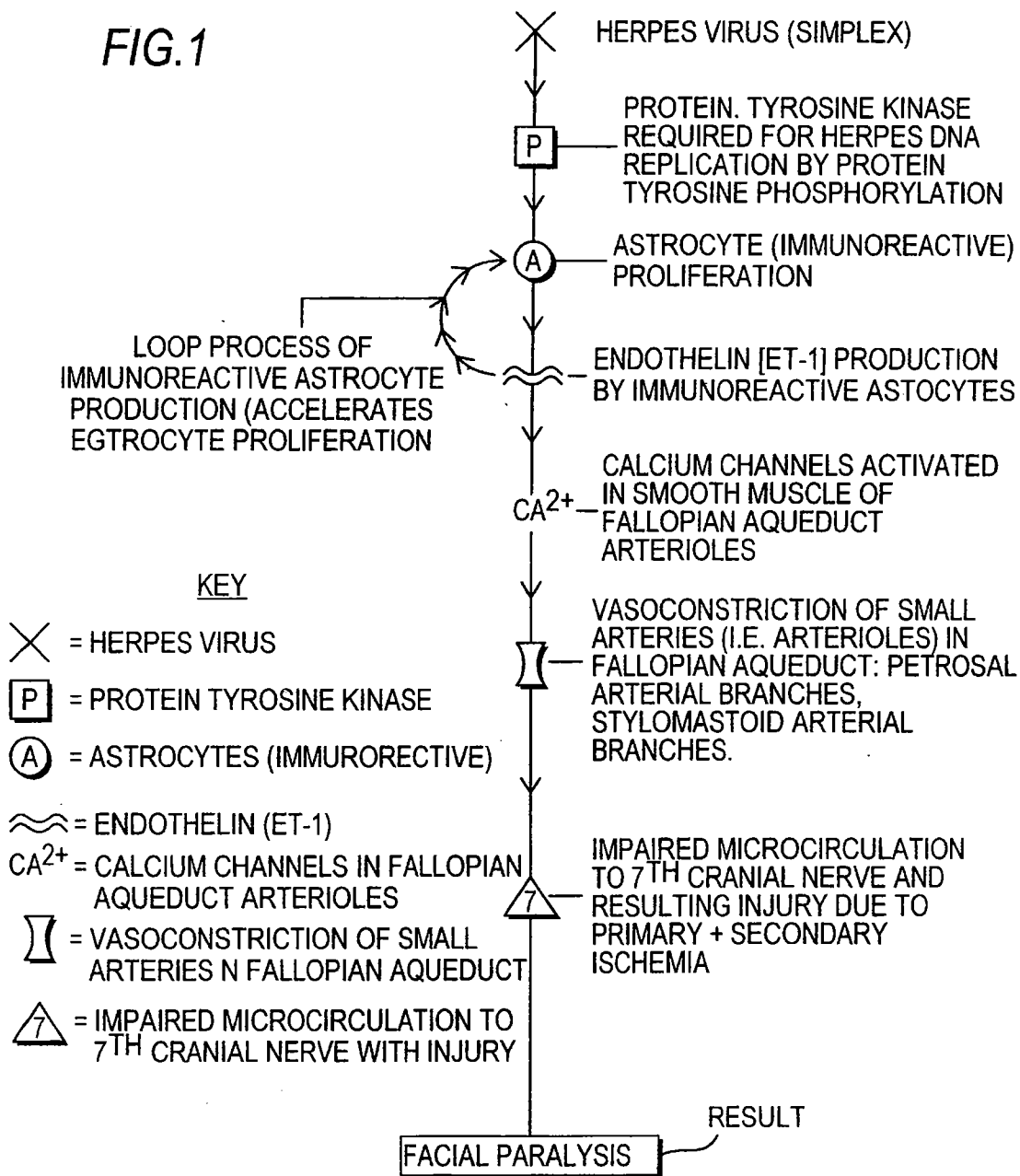
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SCHEMATIC OF PROCESS OF BELL'S PALSY*
PATHOLOGICAL PROGRESSION

FIG. 1



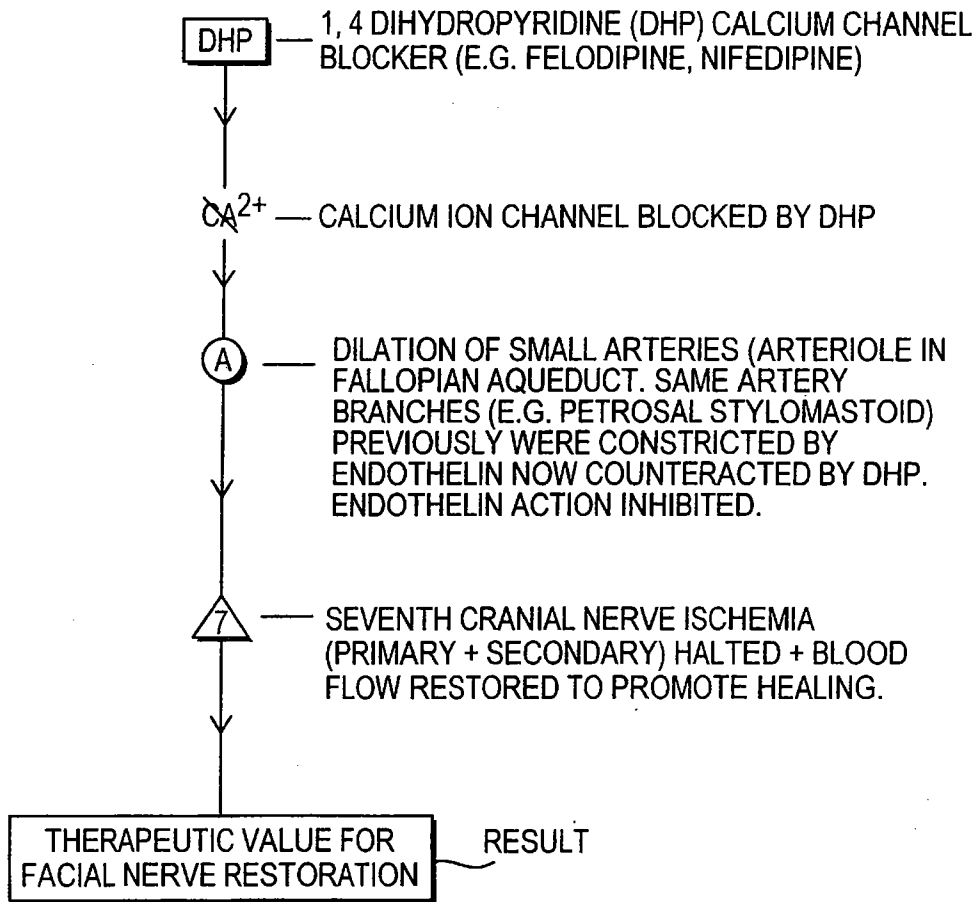
KEY

- ✕ = HERPES VIRUS
- P = PROTEIN TYROSINE KINASE
- ⊙ A = ASTROCYTES (IMMUNOREACTIVE)
- ≈ = ENDOTHELIN (ET-1)
- CA²⁺ = CALCIUM CHANNELS IN FALLOPIAN
AQUEDUCT ARTERIOLES
- ⌋ = VASOCONSTRICTION OF SMALL
ARTERIES IN FALLOPIAN AQUEDUCT
- △ 7 = IMPAIRED MICROCIRCULATION TO
7TH CRANIAL NERVE WITH INJURY

*ALSO APPLIES TO RAMSAY HUNT
INVOLVING HERPES VIRUS (ZOSTER)

SCHEMATIC OF PROCESS OF BELL'S Palsy* WITH DHP CHANNEL BLOCKERS

FIG. 2



KEY

DHP = 1, 4 DIHYDROPYRIDINE CALCIUM CHANNEL BLOCKER (E.G. FELODIPINE)

Ca²⁺ = CALCIUM ION CHANNEL IN AQUEDUCT ARTERIES

(A) = DILATED ARTERIOLES IN AQUEDUCT

(7) = SEVENTH CRANIAL NERVE IN AQUEDUCT

*ALSO APPLIES TO RAMSAY HUNT

**THERAPY FOR HERPES NEUROLOGICAL
VIRAL CONDITIONS UTILIZING 1,4-
DIHYDROPYRIDINE CALCIUM CHANNEL
BLOCKERS**

This patent claims priority of Provisional Application No. 60/065,145 filed Nov. 12, 1997.

FIELD OF THE INVENTION

The present invention relates to the treatment of certain herpes viral neurological conditions in mammals, principally Bell's Palsy, a palsy of the facial nerves, and to the use of calcium channel blockers coupled preferably with a herpes virus antagonist in a treatment therapy. Other herpes conditions include Ramsay Hunt and other herpes caused neurological conditions such as Herpes Simplex Encephalitis.

BACKGROUND OF THE INVENTION

Bell's Palsy (originally described by Charles Bell, 1812) is recognized as a palsy of the facial nerve, generally the seventh cranial nerve. It most commonly affects one side of the face, may be partial or total, and has a progression time of 7 to 10 days. Regarded in the past as idiopathic, there has recently been convincing evidence that it has its cause in the herpes type virus of the simplex type. Some physicians reassure patients that the disease will most likely remit in a period lasting from 3 weeks up to 6 months, (leading some physicians to advocate a no action policy other than facial management, sometimes referred to as "therapeutic nihilism") but the fact remains that about 24% of the victims with current popular therapies are left with some residual paralysis or other aftereffects such as hemi-facial spasm, synkinesis, or loss of tearing or blinking capacity.

An understanding as to the likely physiological events (without an identification of their cause) was comprehensively put forward by Hilger (Hilger J, *The Nature of Bell's Palsy. Laryngoscope*, 54:228-235, 1949) and Blunt (Blunt M, *Possible Role of Vascular Changes in the Etiology of Bell's Palsy, J. Laryngol Otol*, 70:701-713, 1956)) where they maintained that vasoconstriction of the arterioles within the fallopian aqueduct of the temporal bone was responsible for the facial palsy. This vasoconstriction was believed to lead to primary ischemia (tissue anemia) entailing edema of the nerve sheath and a secondary ischemia due to nerve compression. K. Adour opposed this account and instead put forward a viral theory (Adour K K, *Cranial Polyneuritis and Bell's Palsy, Arch Otolaryngol*, 102:262-4, 1976) based on herpes simplex reactivation and maintained that Bell's Palsy was polycranial which was believed to be inconsistent with an ischemia scenario. However, support of the former ischemia outlook was provided through anatomical electromyographical and histopathological studies summarized by U. Fisch (Fisch U. and Felix, H, *On the Parthenogenesis of Bell's Palsy. Acta Otolaryngol*, 95:532-538, 1983)). Further the ischemia description of events fits well with later causal analysis by M. Ikeda (Ikeda M et al, *Plasma Endothelin Level in the Acute Stage of Bell Palsy, Arch Otolaryngol Head Neck Surg*, 122:849-852, August 1996) involving endothelin findings; and work on the immunological role of endothelin has been inferentially linked by the inventor to an ischemia scenario (which requires—a herpes viral role) as will be later explained.

Current therapy mainly involves the administration of steroids, particularly prednisone (see U.S. Pat. No. 2,897, 216) within the first 3 days of onset, where the standard

initial prednisone dosage is about 30 mg. and is tapered off over a 5 day period to a 10 mg. level. In parts of Japan and Europe the steroid treatment has taken the form of heavier steroid dosages, mainly cortisone, incorporated within an IV infusion of low molecular dextran (Kinishi M et al., *Conservative Treatment of Hunt Syndrome, Nippon Jibinkoka Gakkai Kaiho*, 95:1, 65-70, 1992) (See U.S. Pat. No. 2,841,578). The theory underlying steroid treatment, either by prednisone or the higher dosage method, is to improve microcirculation, which has been impaired due to inflammation affecting the seventh cranial nerve. It may be noted that steroid treatment of the high dosage type has its share of hazards that leave many physicians uncomfortable, and which includes serious hepatic and renal disorders.

Recently a new element of approach that is coupled with steroid therapy has emerged from the work of Dr. Kedar Adour, who for many years had maintained that the herpes simplex virus is the original causal agent in Bell's Palsy. Based on this belief, Adour has advocated the use of acyclovir (See U.S. Pat. No. 2,539,963) (commonly used for treating herpes viral infections) for treating Bell's Palsy. He has in this effort conducted a double blind study (Adour K K et al., *Bell's Palsy Treatment. With Acyclovir And Prednisone Compared With Prednisone Alone: A Double-Blind, Randomized Controlled Trial. Otol Rhinol. Laryngol* 1996;105:371-378.) (Kaiser Permanente Medical Center), which provides viable support for the use of acyclovir, an established herpes virus inhibitor. The study compared an acyclovir-prednisone group of subjects with a prednisone-placebo group and the following results were obtained: a 92% volitional motion recovery rate for the acyclovir group versus 76% for the prednisone-placebo group, and an 87% prevention rate of nerve degeneration for acyclovir-prednisone versus 70% for prednisone-placebo. Although the number of subjects was one hundred, about equally split in the 2 groups, results are both statistically significant and in agreement with other studies supporting a herpes simplex or herpes family origins of Bell's Palsy. These studies include the work of Sugita (Sugita T et al, *Facial Nerve Paralysis Induced by Herpes Simplex Virus in Mice: An Animal Model of Acute Transient Facial Paralysis, Ann Otol Rhinol Laryngol* 104(7):574-581, July 1995) inducing apparent Bell's Palsy in mice with herpes simplex and the work of Murakami, pointing chiefly to herpes simplex but sometimes invoking other herpes viruses.

Further, recently there has been a significant study by M. Ikeda (Nihon University School of Medicine, Tokyo Japan) linking endothelin, a peptide of 21 amino acids with Bell's Palsy. This study is yet to receive sufficient attention, however it sheds important light on some of the immediate causal events underlying Bell's Palsy. Endothelin is an extremely potent constrictor of blood vessels, particularly smaller ones, and Ikeda maintains that impairment of microcirculation through primary and secondary ischemia in the fallopian aqueduct (and thereby drawing on the earlier work of Hilger and Blunt) is responsible, but what is new here is the role of endothelin in bringing this about. Ikeda, however, regards the etiology of Bell's Palsy as unknown or idiopathic, and does not offer any causal hypotheses for the high endothelin levels.

There are some other current therapies in addition to steroids, but they do not enjoy a similar popularity, although they are occasionally used in conjunction with it. This includes surgical decompression, more prevalent in previous decades, beginning in the thirties, although sometimes still employed (Jabor M A, *Management of Bell's Palsy, J LA State Medical Soc*, 146(7): 279-283, 1996) where damage is

assessed as extensive. Additionally included is electrical stimulation (also used in previous decades (Devrese P P et al., *Electrotherapy in Facial Paralysis, ORL Otorhinolaryngol Relat Spec*, 1974; 36(2): 94-99) acupuncture and bio-feedback (May M, et al, *Bell's Palsy: Management of Sequelae Using EMG. Rehabilitation, Botulinum and Surgery, Am J Otol*, 10(3):220-229, May 1989)). There appears to be no conclusive studies on these techniques and anecdotal evidence is at best mixed. As for surgery, it has its special hazards, while being based upon the ischemia hypothesis.

In addition to the discussed therapies designed to alleviate or minimize damage, management approaches including eye patches and artificial tears are almost invariably offered to avoid permanent eye damage. Electrical conductivity tests are also used and are of significant value in assessing permanent nerve damage of degeneration. Facial massage is sometimes also recommended to aid in circulation and avoid atrophy once muscle movement returns.

There have been 4 patents (U.S. Pat. Nos. 5,589,183, 5,542,437, 5,148,477, 4,817,628) since 1971 that deal with Bell's Palsy. Of the four, two deal with facial management by mechanical devices, and two are electrically diagnostic for assessment purposes.

Ramsay Hunt syndrome (also known as "herpes zoster oticus") is also caused by a herpes virus, but in this case the herpes zoster virus, as was maintained (the condition) by J. Ramsay Hunt in 1907. Ramsay Hunt syndrome frequently results in facial paralysis involving the seventh cranial nerve (as with Bell's Palsy) but also commonly affects other cranial nerves including the 5th 9th and 10th and 11th). (Further, it should be noted that Ramsay Hunt syndrome as referred to in this invention is Ramsay Hunt Type I, not to be confused with Ramsay Hunt Type II, an entirely different condition which is a rare degenerative neurological disorder characterized by epileptic type fits and myoclonus.) Ramsay Hunt is often accompanied at onset by auricular vesicles, sometimes also found on face, neck or scalp and frequently results in hearing loss (48.2% according to S. Murakami). (Murakami S. et al., *Clinical features and Prognosis of Facial Palsy and Hearing Loss in Patients With Ramsay Hunt, Nippon Jibiinkoka Gakkaio*, 99:12, 1772-1779, December 1996) Intense ear pain and vertigo and tinnitus are also common manifestations. Ramsay Hunt in relation to facial paralysis of the seventh cranial nerve (as with Bell's palsy) is found to have a less favorable recovery profile than the latter (Robillard R B et al., *Ramsay Hunt Facial Paralysis: "Clinical Analysis of 185 Patients, Otolaryngol Head Neck Surg*, 95 (3pt1):292-297, October 1986) Complete recovery rates are estimated at about 52% (Murakami S. *Nippon Jibiinkoka Gakkai Kaiho, December 1996* 99:12, 1772-9) compared with 76% of Bell's palsy.

In conjunction with the early theory of J. Ramsay, the presence of herpes zoster varicella virus has been confirmed more recently in patients having Ramsay Hunt according to studies by Robillard (Robillard R B et al. *Otolaryngol Head Neck Surgery*:292-297, October 1986) and Wackym (Wackym, P A, *Molecular Temporal Bone Pathology: II Ramsay hunt Syndrome, Laryngoscope*, 1997; 107:9 1165-75, September 1997). In Wackym's study the DNA was confirmed in the temporal bone sections in the geniculate ganglia thereby strongly supporting the hypothesis put forth by Ramsay, and which revealingly is within the areas of the temporal bone that Hilger and Blunt maintained are affected in Bell's palsy namely the petrosal and stylomastoid arteries. In recent years the use of acyclovir has been used often in combination with prednisone (Murakami, S et al.,

Treatment of Ramsay Hunt Syndrome with Acyclovir Prednisone, Significance of Early diagnosis and Treatment, Ann. Neuro; 41(3): 353-357, March 1997) in order to treat Ramsay Hunt, paralleling this current treatment of Bell's palsy. Steroid therapy has also been applied (Adour K K and Hetzler D G, *Current Treatment for Facial Palsy, Am J Otol*, 5(6):499-502, October 1984) as well as the use of other therapies discussed for Bell's Palsy i.e. surgical decompression and electrical stimulation. As with Bell's palsy, there is no conclusive studies on these techniques and anecdotal evidence is at best mixed for this more severe condition. Eye patch treatments due to loss of blinking reflex have been incorporated as in Bell's palsy. Further with regard to the vertigo of Ramsay Hunt, diazepam has been utilized to control this symptom. In summation there is a clear overlap of Ramsay Hunt with Bell's Palsy with regard to past theory and proposed treatment.

BRIEF DESCRIPTION OF THE INVENTION

The present invention is directed to the alleviating the effects of Bells Palsy and Ramsay Hunt as well as other herpes caused neurological conditions by providing a therapy that directly addresses the mechanisms believed to cause the ailment. The invention was realized by an analysis of the existing medical literature on the disease and by developing what the inventor believes to be a novel coherent perspective identifying the most significant causation factors and by determining a pharmacology directed to affecting those factors. Thus, although the invention has been achieved without experimentation on humans, it represents the results of an analysis of medical and pharmacological considerations not previously reported for the treatment of a very serious and debilitating ailment. Although logically arrived at, the invention is not the result of merely following markers laying out the path to its discovery in the existing literature.

The therapy disclosed in this application will rest on a proposed causal hypothesis involving both endothelin and herpes simplex virus for Bell's palsy and other herpes virus for other conditions (e.g. herpes zoster for Ramsay Hunt). Calcium channel blockers that are of the 1,4-dihydropyridine derivative class, especially felodipine but also including nifedidine, nimodipine (See U.S. Pat. No. 3,799,934), nisoldipine (See U.S. Pat. No. 4,154,839) or alenodipine may be utilized to treat Bell's Palsy and other herpes causing neurological conditions. The treatment is proposed as continuing up to the tenth day of progression, but to be started as early as possible. The treatment is based on a proposed dynamic for the pathological process underlying Bell's Palsy and the other conditions. The proposed therapy is designed to counter the effects of this pathological process as well as inhibit the very process itself. In a further embodiment, acyclovir, a herpes virus antagonist that can stem herpes viral DNA replication may be used in support of the DHP treatment.

The pathological process supported is the pathological process described by Hilger and Blunt in which vasoconstriction of arterioles in the fallopian aqueduct of the temporal bone; however, it is here suggested that this process is itself brought about by an immunoreactive response to a herpes virus, mainly the herpes simplex virus. This response entails the production of the peptide endothelin, one of the most potent natural vasoconstrictors known. Endothelin achieves its vasoconstriction through the release of calcium ions (CA2+) into the smooth muscle tissue of arteries, particularly the smaller arteries (arterioles). The vasoconstriction which results impairs microcirculation to the facial nerve (seventh cranial nerve) by primary and secondary ischemia.

The use of DHP calcium channel blockers, particularly felodipine, nifedipine, nimodipine, or nisodipine should result in (1) rapid vasodilation of the aqueduct arterioles (2) reduced resistance in the arterioles (3) the blocking of the same channel through which endothelin acts and therefore functionally impairing endothelin's mechanism for generating vasoconstriction. Adequate circulation should then follow with blood and oxygen flow to the seventh cranial nerve. The restoration of adequate microcirculation should then avert further damage and allow immediate blood flow to promote healing. This treatment should compare favorably to current popular steroid approach in that it precisely targets the pathological process, rather than deploying a general anti-inflammatory agent to achieve dilation. Steroid use should only be effective to the extent it counters the effects of a high endothelin level, which it does only indirectly as an anti-inflammatory agent. Felodipine is particularly suited for a more direct and effective role since in comparison studies with other DHP calcium channel blockers in treating hypertension it is more effective in its arterial action. Moreover, it has been shown to effect arterioles of the order of size found by arterioles in the fallopian aqueducts. Further, it is designed to selectively effect smooth muscle as opposed to cardiac and smooth muscle (nifedipine) which is the main component of the smaller arteries (i.e. arterioles) which comprise the fallopian aqueduct. Additionally, prednisone as well as other steroids contain various known hazards including hepatic and renal disorders. The steroids are also immunosuppressive agents and inhibit processes needed for combating any herpes infection. Moreover, in contrast to other proposed therapies such as electrical stimulation and biofeedback, the DHP calcium channel blocker therapy is based on a consideration of a viable understanding of the Bell's Palsy pathological process and its dynamics. Surgery also has various hazards with limited success and has consequently diminished in use over recent years.

The same dynamics and treatment regimen involving 1,4 DHP Dihydropyridine calcium channel blockers proposed here for Bell's Palsy would also lend itself to treatment of Ramsay Hunt. The vasoconstriction of arterioles in the fallopian aqueduct would result in primary and secondary ischemia with all the mentioned microcirculatory problems in both conditions, although in Ramsay Hunt the herpes zoster virus rather than the herpes simplex is the initiating causal factor. However, the same 1,4-dihydropyridine calcium channel blockers should counter and inhibit the pathological process in light of the parallel vasoconstriction of the same arterioles mentioned previously for the studies by P. Wackmyn and R B Robillard. Further, there is some evidence that endothelin (ET-1) can be specifically linked to an immunological reaction to the herpes zoster virus and other herpes virus (Smith R F and Smith T F, *Identification of New Protein Kinase in Three Herpes Viruses*, *J Virol*, 63:1, 450-455, January 1989) and also involve astrocytes (Kuo-Chun Ma et al., *Reactive astrocytes in Viral Infections of the Human Brain Express Endothelin-Like Immunoneoactivity*, *J Neurol Sci*, 126, 184-192, November 1994) as vital agents in the process.

Similarly the invention strongly suggests other herpes viral conditions such as herpes simplex encephalitis may be similarly treated insofar as similar viruses, vasoconstriction, endothelin and astrocytes (Kuo-chun Ma) may be involved.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic of process of Bell's Palsy Pathological Progression and may also serve as a model for other herpes causing neurological conditions e.g. Ramsay Hunt.

FIG. 2 is a schematic of the proposed therapy of Bell's Palsy with DHP Calcium Channel Blockers, and a model for the other herpes causing neurological conditions e.g. Ramsay Hunt.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The proposed therapy should be administered as soon as possible upon the first diagnosis of Bell's Palsy or other herpes causing neurological conditions and continue up to the tenth day after first symptoms. Damage as mentioned may be regarded as being brought about by primary and secondary ischemia originating in vasoconstriction of blood vessels in the fallopian aqueduct; consequently, the earlier that microcirculation to the seventh cranial nerve may be restored within the aqueduct, the sooner further damage could be averted as well as natural healing processes activated. The vasoconstriction brought about by endothelin action may involve such arteries and their branches as the petrosal artery branches (Fisch U. and Felix H., *On the Parthenogenesis of Bell's Palsy*, *Acta Otolaryngol*, 95:532-538, May 1983; Blunt M, J. *Laryngol Otol*, 70:701-713, 1956 and stylomastoid artery (Blunt M. J. *Laryngol Otol.*, 1956); Hilger J, *Laryngoscope.*, 54:228-235, 1949). DHP calcium channel blockers are preferred for their vasodilatory capacity and in the reduced peripheral resistance that they offer to blood flow, resulting from their blocking action of calcium ions channels, the very channels stimulated by endothelin to produce calcium ions.

A preferred embodiment is to use felodipine, which is selective to smooth vascular muscle tissue, the very tissue comprising the arterioles (composed mainly of smooth muscle tissue) the vessels most effected in the vasoconstriction of Bell's Palsy. Due to felodipine's selectivity and other characteristics felodipine is especially suited as a promising Bell's Palsy treatment agent. These characteristics include its effect on smaller arterioles of the magnitude found in the fallopian artery networks, as well as its consistent superior effectiveness (Hagiwara S et al., *Effects of Felodipine, Nifedipine and Verapamil on Cystolic Ca²⁺ on Contraction of Smooth Muscle Tissue*, *Eur Journal Pharmacol*, 234(1):1-7, March 1983) in vasodilation found in blood pressure reduction by felodipine compared with nifedipine. The blood brain barrier which may limit the effectiveness in reaching these arteries (although somewhat borderline in their location) is also penetrated rather well by felodipine as clinically supported.

Another embodiment of the present invention is to employ nifedipine, which has been proven effective against angina for relief of spasm of arteries or arterioles as well as being selective to both coronary and smooth muscle.

Nisodipine, another DHP calcium channel blocker acting on the same sites is effective in much lower dosage levels than felodipine and also avoids the coronary areas.

Nimodipine, a dihydropyridine (DHP) used to treat SAG hemorrhaging is most effective in this latter capacity. Further, it may be noted that tests in countering the effects of endothelin were primarily done with respect to nifedipine (Kiowaski W. et al., *Endothelin-induced Vasoconstriction in Man; Variable Modification caused by endothelium-Derived Relaxing Factor*, *Schweiz Med Wochenschr*, 122:15:559-562, April 1992; Meyer, P et al., *Effects of Calcium Channel Blockers on the Response to Endothelin-1, Bradykinin and Sodium Nitroprusside in Porcine Ciliary Arteries.*, *Exp Eye Res*, 60:5: 505-10, May 1995) Significantly, however, there is a 1996 study (Drimal J. and