US008450379B2

(12) **United States Patent**
Belanoff

(10) **Patent No.: US 8,450,379 B2**
(45) **Date of Patent: May 28, 2013**

(54) **METHODS FOR TREATING MIGRAINE**

(75) Inventor: **Joseph K. Belanoff**, Woodside, CA (US)

(73) Assignee: **Corcept Therapeutics, Inc.**, Menlo Park, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1041 days.

(21) Appl. No.: **10/703,069**

(22) Filed: **Nov. 5, 2003**

(65) **Prior Publication Data**

US 2004/0132703 A1 Jul. 8, 2004

Related U.S. Application Data

(60) Provisional application No. 60/424,199, filed on Nov. 5, 2002.

(51) **Int. Cl.**
A61K 31/045 (2006.01)
A61K 31/05 (2006.01)

(52) **U.S. Cl.**
USPC **514/729**; 514/724; 514/730; 514/731; 514/732; 514/733

(58) **Field of Classification Search**
USPC 514/179, 729–733, 724
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,250,529	A *	10/1993	Theoharides	514/254.07
5,468,741	A	11/1995	Yen	
5,521,166	A *	5/1996	Grubb	514/170
6,166,013	A *	12/2000	Coghlan et al.	514/239.5
6,380,223	B1 *	4/2002	Dow et al.	514/357
6,579,898	B2	6/2003	Humphrey	
6,589,947	B1 *	7/2003	Hamanaka et al.	514/183
2003/0148987	A1 *	8/2003	Morris et al.	514/44

FOREIGN PATENT DOCUMENTS

WO	WO 98/03179	A	1/1998

OTHER PUBLICATIONS

Hardman et al. "The pharmaceutical Basis of Therapeutics," 1996, pp. 1430-1431.*

Morgan et al. "Dscovery of potent, nonsteroidal, and highly selective glucocorticoid receptor antagonists," J. Med. Chem. Jun. 2002, vol. 45, No. 12, pp. 2417-2424.*

The Merck Manual, fifteenth edition, 1987, pp. 1355-1356.*

Kettel, L.M. et al; "Endocrine Responses to Long-Term Administration of the Antiprogesterone TU-486 in Patients with Pelvic Endometriosis"; *Fertility and Sterility*; 1991; pp. 402-407; vol. 56, No. 3; (Abstract from database BIOSIS on ACS; Accession No. 1991:505867).

Adelman, J., et al., "Current options for the prevention and treatment of migraine," *Clinical Therapeutics*, vol. 23(6): 772-788 (Jun. 2001).

Agarwal, M.K., "The antiglucocorticoid action of mifepristone," *Pharmacology and Therapeutics*, vol. 70(3): 183-213 (1996).

Sicuteri, F., et al.., "Naloxone effectiveness on spontaneous and induced perspective disorders in migraine," *Headache*, vol. 23(4): 179-183 (1983).

* cited by examiner

Primary Examiner — Shengjun Wang
(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend & Stockton

(57) **ABSTRACT**

This invention relates to the discovery that agents capable of inhibiting the biological action of the glucocorticoid receptor can be used in methods for treating migraine in a subject.

8 Claims, No Drawings

METHODS FOR TREATING MIGRAINE

CROSS REFERENCES TO RELATED APPLICATIONS

This application claims priority to U.S. 60/424,199, filed Nov. 5, 2002, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

This invention relates to the discovery that agents capable of inhibiting the biological action of the glucocorticoid receptor can be used in methods for reducing, eliminating, or preventing migraine in a subject.

BACKGROUND OF THE INVENTION

Migraine is a common, underdiagnosed, and undertreated neurological disorder. Although migraine is the most common cause of severe, recurring headache, headache is only one of them any ways the disease manifests itself. Migraine may also include visual disturbances, alterations in consciousness, photophobia, or phonophobia. The condition can be truly debilitating and the pain can interfere with a person's ability to live a normal productive life. Indeed, attacks can force the sufferer to abandon everyday activities for up to 3 day. Even in symptom-free period, sufferers may live in fear of the next attack.

More than 23 million Americans older than 12 years of age experience migraine, with a 17.6% prevalence in females and 5.7% in males. Given the high prevalence of sufferers, it is not surprising that American businesses lose upwards of 50 billion dollars annually because of absenteeism, reduced worker productivity, and medical expenses secondary to migraine. Thus, the economic and social consequences of migraine are enormous.

Of the different types of migraines, classical migraine (migraine with aura) and common migraine (migraine without aura) are the two most prevalent. Although migraine is caused by intermittent brain dysfunction, the precise pathophysiological mechanisms involved are not understood.

Drugs that have been used in an attempt to treat migraine include: ergotamine and ergotamine-like agents; serotonin agonists; and caffeine with ergots or other pharmacologic agents (see e.g., Silberstein, S. D., Curr. Opinion Neurology 7:258-263 (1994); Welch, K. M. A., New Engl J. Med. 329: 1476-1483 (1993); Dumar, K. L., J. Gen. Int. Med. 9:339-348 (1994); Saadah, H., Headache 32:95-97 (1992); and Becker, Arzneimittelforshung (42(4):552-555 (1992)). All of these drugs are thought to initially relieve migraine-associated pain by causing vasoconstriction. Unfortunately, this leads to numerous side effects such as chest pain or pressure, flushing, generalized tingling sensations, nausea, vomiting, pain in the legs and arms, asthenia, drowsiness, and dizziness. Acute ergotism is a particularly pernicious side effect of ergot drugs and is characterized by severe central and peripheral vasoconstriction, nausea, vomiting, diarrhea, colic, headache, vertigo, paresthesia, and possibly convulsive seizures.

Patients have, on occasion, found total or partial relief for some forms of migraine through the use of non-prescription analgesics. As outlined by Welch (New Engl J. Med. 329: 1476-1483 (1993)), the initial dosages of such analgesics are typically: aspirin, 500-650 mg; acetaminophen, 500 mg; naproxen sodium, 750-825 mg; tolfenamic acid, 200-400 mg; and, ibuprofen 200 mg. However, the absorption of these and other agents during a migraine attack has been shown to be impaired, apparently due to gastric stasis.

While significant advances have been made in dealing with migraine, none has proven to be broadly effective for an extended time frame, since the side effects associated with the various options limits their value.

Clearly, there is a need in the art for an effective migraine treatment. Ideally a migraine drug formulation should be nonaddictive and free of vasoactive agents. This requires the exclusion of ergots, serotonin agonists such as sumatriptan, and caffeine. The formulation should relieve or eliminate migraine symptoms, and should be effective when used for acute treatment or when used prophylactically. The invention disclosed herein meets these and other needs. The current invention is based, at least in part, on the surprising discovery that glucocorticoid receptor antagonists are effective agents for the treatment of migraine.

Corticosteroids are steroid hormones released by the adrenal glands. The most significant human adrenal corticosteroids are cortisol, corticosterone and aldosterone. Corticosteroids produce cellular effects following binding to receptors located in the cytoplasm of the cell. Two general classes of corticosteroid receptors are now recognized, the mineralocorticoid receptors (also termed type I, or MR) and the glucocorticoid receptors (also termed type II, or GR).

Mineralocorticoid receptors (MRs) bind cortisol with tenfold higher affinity than glucocorticoid receptors (GRs) bind glucocorticoids. Thus, the activation of the two classes of receptors may differ depending on the corticosteroid (cortisol) concentration. Blood levels of the glucocorticoid cortisol vary over a wide range during the day. In general, normal cortisol concentrations in the blood range from about 0.5 nM to about 50 nM; however, in response to stress, cortisol concentration may exceed 100 nM.

Glucocorticoid blockers are agents that block or reduce the effects of glucocorticoids. Such interference with glucocorticoid action may, for example, be due to interference with binding of glucocorticoid agonists to glucocorticoid receptors (GR), or to interference with the action of agonist-bound GR at the cell nucleus, or to interference with expression or processing of gene products induced by the action of agonist-bound GR at the nucleus. Glucocorticoid receptor antagonists (GR antagonists) are compounds which inhibit the effect of the native ligand or of glucocorticoid agonists on GR. One mode of action of GR antagonists is to inhibit the binding of GR ligands to GR. A discussion of glucocorticoid antagonists may be found in Agarwal et al. "Glucocorticoid antagonists", FEBS Lett., 217:221-226 (1987). An example of a GR antagonist is mifepristone, (11β,17β) 11[4 (dimethylamino) phenyl]-17 hydroxy-17 (1 propynyl)estra-4,9 dien-3 one, also known as RU-486 or RU-38486. See U.S. Pat. No. 4,368, 085. Mifepristone binds specifically to GR with an affinity about 18 times that of the affinity of cortisol for GR. GR antagonists may be steroids, such as mifepristone, or non-steroids.

The present inventors have determined for the first time that glucocorticoid receptor antagonists are effective agents for the treatment of migraine. Thus, the present invention fulfills the need for an effective method for the treatment of migraine by providing methods of administering glucocorticoid receptor antagonists to a subject.

BRIEF SUMMARY OF THE INVENTION

The present invention is based at least in part, upon the discovery that administration of a glucocorticoid receptor antagonist provides an effective and of improved treatment of

migraine. Thus, in one aspect, the invention is directed toward methods of treating migraine in a subject, provided that the subject is not otherwise in need of treatment with a glucocorticoid receptor antagonist, and provided that the subject is not also being treated with triptans nor any other pharmaceutically prescribed entity that is predominantly metabolized by a cytochrome P450-3A4 isoenzyme.

In one aspect of the invention, the glucocorticoid receptor antagonist comprises a steroidal skeleton with at least one phenyl-containing moiety in the 11-beta position of the steroidal skeleton. In one aspect, the phenyl-containing moiety in the 11-beta position of the steroidal skeleton is a dimethylaminophenyl moiety. In another aspect, the glucocorticoid receptor antagonist is mifepristone.

In one aspect of the present invention, the glucocorticoid receptor antagonist is selected from the group consisting of 11β-(4-dimethylaminoethoxyphenyl)-17α-propynyl-17β-hydroxy-4,9-estradien-3-one and 17β-hydroxy-17α-19-(4-methylphenyl)androsta-4,9(11)-dien-3-one. In another aspect, the glucocorticoid receptor antagonist is selected from the group consisting 4α(S)-Benzyl-2(R)-prop-1-ynyl-1,2,3,4,4α,9,10,10α(R)-octahydro-phenanthrene-2,7-diol and 4α(S)-Benzyl-2(R)-chloroethynyl-1,2,3,4,4α,9,10,10α(R)-octahydro-phenanthrene-2,7-diol.

In another one aspect, the glucocorticoid receptor antagonist is (11β,17β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one.

In another aspect of the present invention, the glucocorticoid receptor antagonist is administered in a daily amount of between about 0.5 to about 35 mg per kilogram of body weight per day. In another aspect, the glucocorticoid receptor antagonist is administered in a daily amount of between about 5 to about 15 mg per kilogram of body weight per day.

In one aspect of the present invention, the administration is once per day. In yet another aspect, the mode of administration is by a transdermal application, by a nebulized suspension, or by an aerosol spray. In another aspect, the mode of administration is oral.

In another aspect the invention also provides a kit for treating migraine in a subject. The kit comprises a specific glucocorticoid receptor antagonist and an instructional material teaching the indications, dosage and schedule of administration of the glucocorticoid receptor antagonist to a patient suffering from migraine.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "migraine" refers to a symptom complex occurring periodically that is characterized by one or more of the following symptoms: pain in the head that may be exacerbated by movement or physical activity; nausea and/or vomiting, diarrhea, photophobia, visual disturbances including scintillating appearances of light; alterations in consciousness including seizure, syncope, and confused state; vertigo, light headedness, scalp tenderness, or paresthesia. The particular combination of symptoms and their frequency and severity are used to classify migraine into numerous subclasses (see, e.g. Headache Classification Committee of the International Headache Society: *The International Classification of Headache Disorders,* 2nd edition. Cephalalgia 24, supplement 1, 2004; available from Blackwell Publishing, 9600 Garsington Road, Oxford OX4 2DQ, UK). Not every migraine needs to meet all migraine criteria to be classified as migraine. For example, a person may have a left-temporal throbbing headache of moderate intensity worsened by physical activity. These headache features meet migraine criteria. However, this headache may not be accompanied by nausea or hypersensitivity to light or noise and, therefore, not fulfill all the criteria for migraine. Yet, if some of this person's other headaches meet all the migraine criteria, then one can say that this headache is also a migraine.

The term "migraine attack" refers to the experience of migraine symptoms. The experience may include the early premonitory symptoms, as well as any symptoms that occur during a migraine.

The term "headache" refers to pain in various parts of the head, not confined to the area of distribution of any nerve. Many types of headaches are known. For example, the classification system published by the Headache Classification Committee of the International Headache Society (IHS) in 1988 lists more than 100 types of headache (Headache Classification Committee of the International Headache Society: *The International Classification of Headache Disorders,* 2nd edition., supra).

The term "prophylactic" refers to an agent that acts to prevent disease, such as migraine. In one aspect, a glucocorticoid receptor antagonist of the invention is administered prophylactically to prevent the onset of migraine.

The terms "treating", "treatment", "to treat" refer to means for preventing, reducing, or eliminating migraine and or the accompanying symptoms in a subject. Treatment refers to any indicia of success in prevention, reduction, elimination, or amelioration of migraine, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms, prevention, or lessening of migraine symptoms or making the condition more tolerable to the subject; making the migraine less debilitating; or improving a patient's physical or mental well-being. For example, success of treatment by methods of the invention could be measured by comparing the frequency and severity of migraine attacks in the year before treatment with anti-glucocorticoids of the invention was initiated, with the year following the initiation of treatment. The prevention, treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, or personal interview regarding symptom severity and quality of life, or any other appropriate means known in the art.

The term "cortisol" refers to a family of compositions also referred to as hydrocortisone, and any synthetic or natural analogues thereof.

The term "glucocorticoid receptor" ("GR") refers to a family of intracellular receptors also referred to as the cortisol receptor, which specifically bind to cortisol and/or cortisol analogs. The term includes isoforms of GR, recombinant GR and mutated GR.

The term "mifepristone" refers to a family of compositions also referred to as RU486, or RU38.486, or 17-β-hydroxy-11-β-(4-dimethyl-aminophenyl)-17-α-(1-propynyl)-estra-4,9-dien-3-one), or 11-β-(4dimethylaminophenyl)-17-β-hydroxy-17-α-(1-propynyl)-estra-4,9-dien-3-one), or analogs thereof, which bind to the GR, typically with high affinity, and inhibit the biological effects initiated/mediated by the binding of any cortisol or cortisol analogue to a GR receptor. Chemical names for RU-486 vary; for example, RU486 has also been termed: 11β-[p-(Dimethylamino)phenyl]-17-β-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one; 11β-(4-dimethyl-aminophenyl)-17β-hydroxy-17α-(prop-1-ynyl)-estra-4,9-dien-3-one; 17β-hydroxy-11β-(4-dimethylaminophenyl-1)-17α-(propynyl-1)-estra-4,9-diene-3-one; 17β-hydroxy-11β-(4-dimethylaminophenyl-1)-17α-(propynyl-1)-E; (11β,17β)-11-[4-dimethylamino)-phenyl]-

17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one; and 11β-[4-(N,N-dimethylamino) phenyl]-17α-(prop-1-ynyl)-D-4,9-estradiene-17β-ol-3-one.

The term "specific glucocorticoid receptor antagonist" refers to any composition or compound which partially or completely inhibits (antagonizes) the binding of a glucocorticoid receptor (GR) agonist, such as cortisol, or cortisol analogs, synthetic or natural, to a GR. A "specific glucocorticoid receptor antagonist" also refers to any composition or compound which inhibits any biological response associated with the binding of a GR to an agonist. By "specific", we intend the drug to preferentially bind to the GR rather than the mineralocorticoid receptor (MR) with an affinity at least 100-fold, and frequently 1000-fold.

A subject "not otherwise in need of treatment with a glucocorticoid receptor antagonist" is an individual or patient who is not being treated with antiglucocorticoid compounds for any disorder accepted by the medical community to be effectively treatable with antiglucocorticoid compounds. Conditions known in the art and accepted by the medical community to be effectively treatable with glucocorticoid receptor antagonists include: Cushing's disease, drug withdrawal, dementia, stress disorders, anxiety disorders (U.S. Pat. No. 5,741,787), depression, psychotic major depression (U.S. Pat. No. 6,150,349), schizoaffective disorder, diabetes, rheumatoid arthritis, autoimmune disease, HIV infection, dermatitis, inflammation, fibromyalgia, central nervous system disease, neurodegeneration, neural injuries, pelvic pain, and various cancers.

A subject "not also being treated with triptans nor any other pharmaceutically prescribed entity that is predominantly metabolized by a cytochrome P450-3A4 isoenzyme" is an individual or patient who is not also being treated with triptan drugs such as elitriptan or sumatriptan for any disorder accepted by the medical community to be effectively treatable with triptan drugs. Triptan drugs are thought to act through their affect on the metabolic activity of the P450-3A4 enzyme. Thus, a subject "not also being treated with triptans nor any other pharmaceutically prescribed entity that is predominantly metabolized by a cytochrome P450-3A4 isoenzyme" is not being treated with any drugs that affect the metabolic activity of the P450-3A4 enzyme in a manner similar to the manner in which triptan drugs affect the P450-3A4 enzyme.

I. Introduction

This invention pertains to the surprising discovery that agents that can inhibit glucocorticoid-induced biological responses are effective for treating migraine. In treating migraine, the methods of the invention can ameliorate, eliminate, reduce or prevent the symptoms of migraine. In one embodiment, the methods of the invention use agents that act as GR antagonists, blocking the interaction of cortisol with GR, to treat migraine. The methods of the invention are effective in treating migraine in an afflicted patient.

Cortisol acts by binding to an intracellular, glucocorticoid receptor (GR). In humans, glucocorticoid receptors are present in two forms: a ligand-binding GR-alpha of 777 amino acids; and, a GR-beta isoform that differs in only the last fifteen amino acids. The two types of GR have high affinity for their specific ligands, and are considered to function through the same signal transduction pathways.

The biological effects of cortisol, including pathologies or dysfunctions caused by hypercortisolemia, can be modulated and controlled at the GR level using receptor antagonists. Several different classes of agents are able to act as GR antagonists, i.e., to block the physiologic effects of GR-agonist binding (the natural agonist is cortisol). These antagonists include compositions, which, by binding to GR, block the ability of an agonist to effectively bind to and/or activate the GR. One family of known GR antagonists, mifepristone and related compounds, are effective and potent anti-glucocorticoid agents in humans (Bertagna, *J. Clin. Endocrinol. Metab.* 59:25, 1984). Mifepristone binds to the GR with high affinity, with a K of dissociation<10^{-9} M (Cadepond, *Annu. Rev. Med* 48:129, 1997). Thus, in one embodiment of the invention, mifepristone and related compounds are used to treat migraine in a subject.

As the methods of the invention include use of any means to inhibit the biological effects of an agonist-bound GR, illustrative compounds and compositions which can be used to treat migraine in a subject are also set forth. Routine procedures that can be used to identify further compounds and compositions able to block the biological response caused by a GR-agonist interaction for use in practicing the methods of the invention are also described. As the invention provides for administering these compounds and compositions as pharmaceuticals, routine means to determine GR antagonist drug regimens and formulations to practice the methods of the invention are set forth below.

II. Diagnosis of Migraine in a Subject

Migraine is diagnosed by determining whether some of a person's recurrent headaches meet migraine criteria as disclosed in *The International Classification of Headache Disorders,* 2nd edition, Headache Classification Committee of the International Headache Society: Cephalalgia 24, supplement 1, 2004; which is incorporated herein by reference. For example, the diagnostic criteria set forth by the International Headache Society for diagnosis of migraine without aura are shown in Table 1. Migraines without aura are idiopathic syndromes comprising a recurring headache disorder, manifesting in attacks lasting 4-72 hours, in which headaches are typically unilateral, throbbing, of moderate to severe intensity, aggravated by routine physical activity, and accompanied by nausea and intolerance to brightness and noise.

TABLE 1

International Headache Society Diagnostic Criteria For Migraine Without Aura	
A.	At least 5 attacks that fulfill criteria in B, C, D, and E
B.	Headache attacks that last 4 to 72 hrs (untreated or unsuccessfully treated)
C.	Headache has at least 2 of the following characteristics: Unilateral site Pulsating quality Moderate to severe intensity Aggravation by walking stairs or similar routine physical activity
D.	During headache, at least 1 of the following symptoms: Nausea or vomiting (or both) Photophobia and phonophobia No evidence of related organic disease

Similarly, the International Headache Society provides a set of diagnositic criteria for migraine with aura. These diagnostic criteria are shown in Table 2.

TABLE 2

International Headache Society Criteria For Migraine With Aura	
A.	At least 2 attacks that fulfill criteria in B and C
B.	At least 3 of the following 4 characteristics:

TABLE 2-continued

International Headache Society Criteria For Migraine With Aura	
	One or more completely reversible aura symptoms that indicate focal cerebral cortical or brain-stem dysfunction (or both)
	At least one aura symptom develops gradually over more than 4 min or two or more symptoms occur in succession
	No aura symptom lasts more than 60 min
	Headache follows aura in less than 1 hr
C.	No evidence of related organic disease

Most migraines seen in physicians' offices are migraine without aura (formerly called "common migraine") and migraine with aura (formerly called "classic migraine"). Migraine aura without headache is also quite common, and is seen often by ophthalmologists. Neurologists and headache specialists often treat status migrainosus, characterized by a headache phase of over 72 hours. The other migraine types are fully described in *The International Classification of Headache Disorders,* 2nd edition, supra.

Not every migraine needs to meet all of the migraine criteria. For example, a person may have a left-temporal throbbing headache of moderate intensity worsened by physical activity. These headache features meet migraine criteria. However, this headache may not be accompanied by nausea or hypersensitivity to light or noise and, therefore, does not fulfill all the criteria for migraine. Yet, if some of this person's other headaches meet all the migraine criteria, then one can say that this headache is also a migraine.

A meticulous history is helpful in assessing and diagnosing any migraine patient. Useful information regarding the history of a subject patient's headache might include, but would not be limited to: age of onset; family history; site or sites of pain; duration; character; intensity; mode of onset; time between onset to peak pain; temporal profile; aggravating or precipitating factors; alleviating factors; associated neurologic, ophthalmologic and autonomic features; prior and current medication use, caffeine use; history of head trauma; results of prior neuroimaging studies; a complete review of systems; or why the patient is currently seeking medical attention.

III. General Laboratory Procedures

When practicing the methods of the invention, a number of general laboratory tests can be used to assist in the diagnosis, progress and prognosis of the patient with migraine, including monitoring of parameters such as blood cortisol, drug metabolism, brain structure and function and the like. These procedures can be helpful because all patients metabolize and react to drugs uniquely. In addition, such monitoring may be important because each GR antagonist has different pharmacokinetics. Different patients and disease conditions may require different dosage regimens and formulations. Such procedures and means to determine dosage regimens and formulations are well described in the scientific and patent literature. A few illustrative examples are set forth below.

a. Determining Blood Cortisol Levels

The invention may be practiced upon patients with apparently normal levels of blood cortisol. However, since the treatment for migraine comprises administration of a glucocorticoid receptor antagonist, monitoring blood cortisol and determining baseline cortisol levels are useful laboratory tests to aid in the diagnosis, treatment and prognosis of a migraine patient. A wide variety of laboratory tests exist that can be used to determine whether an individual is normal, hypo- or hypercortisolemic. Migraine patients typically have normal levels of cortisol that are often less than 25 μg/dl in the morning, and frequently about 15 μg/dl or less in the afternoon, although the values often fall at the high end of the normal range, which is generally considered to be 5-15 μg/dl in the afternoon.

Immunoassays such as radioimmunoassays are commonly used because they are accurate, easy to do and relatively cheap. Because levels of circulating cortisol are an indicator of adrenocortical function, a variety of stimulation and suppression tests, such as ACTH Stimulation, ACTH Reserve, or dexamethasone suppression (see, e.g., Greenwald, *Am. J. Psychiatry* 143:442-446, 1986), can also provide diagnostic, prognostic or other information to be used adjunctively in the methods of the invention.

One such assay available in kit form is the radioimmunoassay available as "Double Antibody Cortisol Kit" (Diagnostic Products Corporation, Los Angeles, Calif.), (*Acta Psychiatr. Scand.* 70:239-247, 1984). This test is a competitive radioimmunoassay in which ^{125}I-labeled cortisol competes with cortisol from an clinical sample for antibody sites. In this test, due to the specificity of the antibody and lack of any significant protein effect, serum and plasma samples require neither preextraction nor predilution. This assay is described in further detail in Example 2, below.

b. Determination of Blood/Urine Mifepristone Levels

Because a patient's metabolism, clearance rate, toxicity levels, etc. differs with variations in underlying primary or secondary disease conditions, drug history, age, general medical condition and the like, it may be necessary to measure blood and urine levels of GR antagonist. Means for such monitoring are well described in the scientific and patent literature. As in one embodiment of the invention mifepristone is administered to treat migraine, an illustrative example of determining blood and urine mifepristone levels is set forth in the Example below.

c. Other Laboratory Procedures

Laboratory tests monitoring and measuring GR antagonist metabolite generation, plasma concentrations and clearance rates, including urine concentration of antagonist and metabolites, may also be useful in practicing the methods of the invention. For example, mifepristone has two hydrophilic, N-monomethylated and N-dimethylated, metabolites. Plasma and urine concentrations of these metabolites (in addition to RU486) can be determined using, for example, thin layer chromatography, as described in Kawai *Pharmacol. and Experimental Therapeutics* 241:401-406, 1987.

IV. Glucocorticoid Receptor Antagonists to Treat Migraine in a Subject

The invention provides for methods for treating migraine a subject utilizing any composition or compound that can block a biological response associated with the binding of cortisol or a cortisol analogue to a GR. Antagonists of GR activity utilized in the methods of the invention are well described in the scientific and patent literature. A few illustrative examples are set forth below.

A. Steroidal Anti-Glucocorticoids as GR Antagonists.

Steroidal glucocorticoid antagonists are administered to treat migraine in various embodiments of the invention. Steroidal antiglucocorticoids can be obtained by modification of the basic structure of glucocorticoid agonists, i.e., varied forms of the steroid backbone. The structure of cortisol can be modified in a variety of ways. The two most commonly known classes of structural modifications of the cortisol steroid backbone to create glucocorticoid antagonists include modifications of the 11-beta hydroxy group and modification of the 17-beta side chain (see, e.g., Lefebvre, *J. Steroid Biochem.* 33:557-563, 1989).

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.