Mifepristone (RU-486) treatment for depression and psychosis: a review of the therapeutic implications

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Abstract: The mechanisms underlying the pathophysiology of severe psychiatric illnesses are complex, involving multiple neuronal and neurochemical pathways. A growing body of evidence indicates that alterations in hypothalamic–pituitary–adrenal (HPA) axis function may be a trait marker in both mood disorders and psychosis, and may exert significant causal and exacerbating effects on symptoms and neurocognition. At present, however, no available treatments preferentially target HPA axis abnormalities, although many drugs do increase feedback-regulation of the HPA axis at the level of the glucocorticoid receptor (GR). This action may in part underpin their therapeutic efficacy. Therapeutic interventions directly targeted at GR function may therefore have clinical benefit. The present review examines the current literature for the clinical utility of GR antagonists (specifically mifepristone) in mood disorders and psychosis. At present, most studies are at the "proof-of-concept" stage, although the results of preliminary, randomized, controlled trials are encouraging. The optimum strategy for the clinical application of GR antagonists is yet to be established, their potential role as first-line or adjunctive treatments being unclear. The therapeutic utility of such drugs will become known within the next few years following the results of larger clinical trials currently underway.

Keywords: mifepristone, RU486, glucocorticoid receptor, cortisol, mood disorders, psychosis, treatment

Introduction

Overview

Dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis has long been implicated in the pathogenesis and etiology of severe psychiatric illness. Studies have found evidence of reduced glucocorticoid receptor (GR) mRNA expression in post-mortem brain tissue samples from patients with mood disorders and psychosis (Knable et al 2001; Webster et al 2002; Lopez et al 2003). Many antidepressant drugs increase GR binding and/or number in brain tissue, suggesting that GR regulation may be one aspect of the therapeutic mechanism of action of antidepressants (and mood stabilizers), and the ability of a drug to regulate GR number may be a good predictor of therapeutic efficacy in patients with hypercortisolemia (McQuade and Young 2000). No drugs primarily or preferentially target the GR for use in psychiatry, although several are at present being examined for this purpose. The present review examines the current literature and proof-of-concept evidence for the clinical utility of GR antagonists (specifically mifepristone) in mood disorders and psychosis.

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Search strategy

In order to include other antiglucocorticoid agents that specifically target the GR, the terms ("mifepristone" or "RU 486" or "RU 38486" or "ORG 34850"' or "ORG 34116" or "ORG 34517") were used in the initial search and combined with the terms ("mood disorders" or "psychosis" or "depression" or "bipolar disorder" or "schizophrenia"). The following databases were searched electronically: EMBASE (1980 to present), Medline (1966 to present), CINAHL (1982 to present), PsycINFO (1887 to present), and ISI Web of Science (1981 to present). Citation lists of relevant studies and reviews were checked for other relevant trials.

Background

The hypothalamic–pituitary–adrenal (HPA) axis

One of the major hormonal systems activated during stress is the HPA axis. Neurones in the paraventricular nucleus (PVN) of the hypothalamus secrete corticotrophin-releasing hormone (CRH) which is transported via the hypothalamo-pituitary portal circulation to the anterior pituitary where adrenocorticotropic hormone (ACTH) is secreted through stimulation of pituitary corticotrophs. ACTH then enters the peripheral circulation and stimulates the adrenal cortex to secrete glucocorticoids: corticosterone in rats, and cortisol in humans.

Cortisol is essential for life. It is involved in the maintenance of glucose production from protein, facilitates fat metabolism, supports responsiveness of the vascular tree, modulates central nervous system function, and profoundly affects the immune system (Berne and Levy 1998). Importantly, it is a major regulator of the physiological stress response, through a negative feedback mechanism via corticosteroid receptors. Two distinct corticosteroid receptor subtypes have been identified: the mineralocorticoid receptor (MR; Type I) and the glucocorticoid receptor (GR; Type II). Both receptor types have been implicated in mediating glucocorticoid feedback (Reul and de Kloet 1985), but there are several differences in the distribution, occupancy, and binding properties of the two receptors that affect their physiological role.

The MR is highly expressed in the limbic system whereas the GR is ubiquitous, being present in both subcortical and cortical structures, with a preferential distribution in the prefrontal cortex (Patel et al 2000). Glucocorticoids bind to the MR with 6–10 times higher affinity than to GR (de Kloet et al 1999). Consequently, at basal levels near complete occupation (~90%) of MRs occurs. GRs, however, are little occupied at this point (~10%), and only during times of high cortisol secretion, such as the circadian peak or during stress, do MRs become saturated and GR occupancy increases (to ~67%–74%) (Reul and de Kloet 1985). GR function is therefore critical in the regulation of the HPA axis at times of glucocorticoid excess and it is now recognized that disruption of this self-regulating system may be a major factor in the pathophysiology of mood disorders and psychosis.

The HPA axis in mood disorders and psychosis

The first observations of an elevation in basal cortisol levels in patients with depression were made almost half a century ago by Board and colleagues, and these observations have been repeatedly replicated (Board et al 1956; Gibbons 1964). It should be noted that the extent of HPA axis dysfunction differs by severity and subtype of depression. For example, a recent study found no evidence of hypercortisolism in women with major depression from a community-based setting (Strickland et al 2002), while pronounced HPA axis dysfunction has been described in depressed subjects with psychotic features (Posener et al 2000). The presence of psychosis may be related to hypercortisolism independently of mood symptoms (Christie et al 1986). Hypercortisolism has also been recognized in symptomatic schizophrenic patients (Ritsner et al 2004; Ryan et al 2004).

Improvements in the methodology utilized has overcome some of the complexities surrounding the profiling of HPA axis dysfunction, revealing alterations in the diurnal pattern of cortisol secretion in depression (Deuschle et al 1997; Posener et al 2000), while employing less precise techniques such as total 24-hour cortisol output can fail to detect dysfunction (Brouwer et al 2005). Similarly, the measurement of the molar ratio of cortisol to other adrenal steroids can reveal differences – in the absence of hypercortisolism per se – in moderately depressed, non-psychotic outpatients (Young et al 2002). The most sensitive tests of HPA axis function, however, are "activating" tests, whereby neuroendocrine responses are measured following pharmacological challenge. These are preferred not only because of their increased sensitivity, but because they elucidate functional changes in the HPA axis at the receptor level.

The GR agonist dexamethasone has been used widely to examine HPA axis negative feedback integrity (Rush et al 1996). An abnormal (nonsuppressed) cortisol response

to dexamethasone administration has been described in schizophrenia (Castro et al 1983; Muck-Seler et al 1999) (but also see Ismail et al 1998) and mood disorders (Rush et al 1996), and may be exacerbated by psychotic features (Duval et al 2000). The combined dexamethasone–corticotrophin-releasing hormone (dex–CRH) test is also abnormal in bipolar patients during relapse and recovery (Schmider et al 1995; Rybakowski and Twardowska 1999; Watson et al 2004). Furthermore, GR abnormalities have been observed in post-mortem studies which show evidence of reduced GR mRNA expression in post-mortem brain tissue samples from patients with bipolar disorder and schizophrenia (Knable et al 2001; Webster et al 2002; Lopez et al 2003).

Consequences of HPA axis dysregulation and implications for treatment

Pronounced neurocognitive dysfunction is frequently described in mood disorder (Porter et al 2003; Thompson et al 2005); this may be worse in patients with psychotic features (Fleming et al 2004). In schizophrenia, the symptomatic clinical profile of the illness is complex and diverse, but neurocognitive impairment is consistently reported and some authors have argued that such impairments may be the cardinal feature of the illness (Elvevag and Goldberg 2000).

Elevated levels of corticosteroids are known to impair learning and memory. This has been demonstrated by acute (Lupien and McEwen 1997; Modell et al 1997) and subchronic (Young et al 1999) administration of exogenous corticosteroids in healthy volunteers and in conditions associated with a chronic elevation of endogenous cortisol levels, for example Cushing's disease (Starkman et al 2001; Forget et al 2002), which is also associated with a high incidence of depression that notably resolves with correction of the hypercortisolemia (Dorn et al 1997). Patients receiving systemic corticosteroid therapy also often exhibit cognitive impairment and, in some instances, symptoms of (hypo)mania, depression, and psychosis (Brown and Chandler 2001). HPA axis dysregulation therefore has been suggested to be one of the principal causes of both low mood and neurocognitive impairment, possibly through interactions with other neurotransmitter system (McAllister-Williams et al 1998; Porter et al 2004).

The known consequences of hypercortisolemia on neurocognitive function and mood, and the central role of corticosteroid receptors in HPA axis regulation, therefore indicate a possible use for antiglucocorticoid drugs and make the GR specifically a potentially viable target for therapeutic intervention.

Mifepristone (RU-486)

Discovery and development

Mifepristone (or RU-486) is a synthetic steroid with both antiprogesterone and antiglucocorticoid properties. The compound is a 19-nor steroid with substitutions at positions C11 and C17 (17 beta-hydroxy-11 beta-[4-dimethylamino phenyl] 17 alpha-[1-propynyl]estra-4,9-dien-3-one) which antagonizes cortisol action competitively at the receptor level (Nieman et al 1985). It was discovered in the early 1980s by the French pharmaceutical company Roussel–Uclaf (Herrmann et al 1982; Jung-Testas and Baulieu 1983). At present it is licenced in the UK for the medical termination of pregnancy (trade name: Mifegyne®; marketing authorization holder: Exelgyn Laboratories, Paris, France). Mifepristone was the first antiprogestin to be developed and it has been evaluated extensively for its use as an abortifacient. The original target for the research group, however, was the discovery and development of compounds with antiglucocorticoid properties (Hazra and Pore 2001), and it is these properties that are of greatest interest for their application in the treatment of severe mood disorders and psychosis.

Pharmacokinetics and pharmacodynamic activity

The pharmacokinetics of mifepristone are dose-dependent in humans (Ashok et al 2002). Due to saturation of the serum-binding capacity, high-dose mifepristone results in nonlinear kinetics, whereas lower doses show a linear pattern (Leminen et al 2003). For example, following administration of doses of 50–800 mg, after the absorption and distribution phase of approximately 4–6 hours, the serum concentration of mifepristone remains in the micromolar range for the next 24–48 hours. Within the dose range of 2–25 mg, serum concentrations of mifepristone, as well as the areas under the concentration–time curves (AUC), increase according to dose (Sitruk-Ware and Spitz 2003).

Following a single oral dose of 600 mg mifepristone, the binding equivalent is present in measurable concentrations 7 days after administration, only decreasing below assay detection limits >7–14 days (Foldesi et al 1996). In this study, the concentration of the mifepristone binding

equivalent reached a peak within approximately 2 hours (doses 200–600 mg), indicating rapid absorption. Peak levels were significantly greater following the 600 mg dose (C_{max} = 12.3 µmol/L vs 200 mg: 6.30 µmol/L), while the bioavailability as assessed by the AUC was significantly greater following 600 mg dose than both 200 and 400 mg. These were not, however, directly proportional to the dose increase (Foldesi et al 1996).

In contrast to mifepristone plasma concentrations, plasma concentrations of its metabolites do increase in a dose-dependent manner when larger doses are administered, so that serum metabolite concentrations are close to, or even in excess of, those of the parent compound (Lahteenmaki et al 1987). These metabolites have some antiprogestin and antiglucocorticoid properties, and therefore may mediate some of the actions of mifepristone (Spitz and Bardin 1993).

Side effects of chronic mifepristone administration

Laue and colleagues reported that in healthy male normal volunteers who received mifepristone (10 mg/kg/day), 8 of 11 subjects developed generalized exanthem after 9 days. One subject developed symptoms and signs consistent with the diagnosis of adrenal insufficiency (Laue et al 1990). For immune function, it was reported that total white blood cell counts, absolute lymphocyte, neutrophil, and eosinophil counts, erythrocyte sedimentation rate, and quantitative immunoglobulins did not change. Similarly, T-, B-, and natural killer cell subsets did not change during treatment. Furthermore, functional evaluation of lymphocyte cytotoxicity and proliferation revealed no changes.

A study using lower doses (200 mg/day for 2 to >31 months) in 14 patients with unresectable meningiomas reported milder side effects. Most commonly, fatigue was noted in 11 of the 14 patients (Grunberg et al 1991). However, in a study of mifepristone (200 mg/day for up to 8 weeks) in chronic depression, 1 of 4 patients discontinued treatment prematurely because of the appearance of a rash (Murphy et al 1993). In patients with psychotic depression receiving mifepristone (50–1200 mg/day for 7 days), 2 of 10 patients in the 600-mg group and 1 of 9 in the 1200-mg group reported uterine cramping, while 1 of 11 patients in the 50-mg group and 1 of 9 patients in the 1200-mg group (but none in the 600-mg group) reported a rash. In both cases, this had abated 1–2 months after study completion (Belanoff et al 2002).

Antiglucocorticoid effects of mifepristone

A large amount of human clinical data on the antiglucocorticoid actions of mifepristone have come from studies in Cushing's disease (Sartor and Cutler 1996). Nieman and colleagues administered mifepristone orally at increasing doses of 5, 10, 15, and 20 mg/kg/day for a 9-week period to a patient with Cushing's syndrome due to ectopic ACTH secretion. Following treatment, the somatic features associated with Cushing's syndrome ameliorated and blood pressure normalized. Importantly, suicidal ideation and depression also resolved, and all biochemical glucocorticoid-sensitive parameters normalized (Nieman et al 1985).

Mifepristone has also been shown to rapidly reverse acute psychosis in Cushing's syndrome (van der Lely et al 1991). More recently, high-dose (up to 25 mg/kg/day), long-term mifepristone administration was shown to normalize all biochemical glucocorticoid-sensitive measurements, as well as significantly reverse psychotic depression in a patient with Cushing's syndrome caused by an ACTH-secreting pituitary macroadenoma (Chu et al 2001). Although the adrenal axis also normalized, the 18-month-long mifepristone treatment course led to the development of severe hypokalemia (attributed to excessive cortisol activation of MRs), which responded to spironolactone administration.

Use of mifepristone in mood disorders and psychosis (Table 1)

Early work highlighted the potential for antiglucocorticoid strategies in depression. Initially the focus of studies utilizing mifepristone was on the effect on endocrine parameters (Kling et al 1989; Krishnan et al 1992). In the first open trial of mifepristone treatment of major depression, Murphy and colleagues administered mifepristone (200 mg each morning) for as long as it was tolerated, for up to 8 weeks to 4 patients with "drug-resistant" depression. Data were presented as a case-series and showed improvements of between 16% and 66% on the Hamilton Depression Rating Scale (HDRS) (Murphy et al 1993). The trial terminated, however, due to problems obtaining the trial medication (the supplier cancelled the contract).

Recent studies have renewed interest in the potential therapeutic efficacy of GR antagonists in the treatment of mood disorders and psychosis.

Table 1 Studies of glucocorticoid receptor antagonists in mood disorders and psychosis (see text for further details)

Study	Drug	Dose	Study design	N	Patient group	Concomitant medications	Effects on symptoms	Effects on neurocognitive function
(Kling et al 1989)	Mifepristone	10 mg/kg single dose	[a]Experimental	8	MDD	Drug-free (2 weeks)	n/a	n/a
(Krishnan et al 1992)	Mifepristone	400 mg single dose	[a]Experimental	7	MDD	Drug-free (1 week)	n/a	n/a
(Murphy et al 1993)	Mifepristone	200 mg/day, up to 8 weeks	Open-label	4	MDD	Drug-free; benzodiazepines and acetaminophen permitted	HDRS scores decreased between 16% and 66% for all patients.	n/a
(Høyberg et al 2002)	ORG34517	150–300 mg/day, 450–600 mg/day, up to 4 weeks	Double-blind, randomized, paroxetine controlled	142	MDD	Drug-free; benzodiazepines permitted	All groups improved. Larger improvement from baseline in low-dose ORG group at day 10. Patients reaching full remission significantly higher in low- than both the high-dose and paroxetine-treated groups (39.1% vs 20.5% and 31.0% respectively).	n/a
(Belanoff et al 2001)	Mifepristone	600 mg/day, 4 days	Double-blind, placebo controlled, crossover	5	Psychotic MDD	Antipsychotic free (3 days); benzodiazepines and acetaminophen permitted	HDRS scores declined during mifepristone treatment in all patients. BPRS scores declined in 4 of 5 patients.	n/a
(Belanoff et al 2002)	Mifepristone 1200 mg/day, 7 days	50, 600,	Open-label	30	Psychotic MDD	Stable for 1 week prior	HDRS response by dose in 2/11 (18.2%) 5/10, (50%), 3/9 (33%) patients respectively. BPRS response in 4/11 (36.4%), 7/10 (70%), 6/9 (66.7%) respectively.	n/a
(Simpson et al 2005)	Mifepristone	200 mg tid, 6 days	Open-label	20	Psychotic MDD	Drug-free (1 week) except for lorazepam	CGI and HDRS improved after week 1, and between week 1 to 4. BPRS improved after week 4	n/a
(Young et al 2004)	Mifepristone	600 mg/day, 7 days	Double-blind, placebo controlled RCT	20	Bipolar disorder (depressed)	Stable for 6 weeks prior	HDRS (5.1 points), MADRS (6 points), BPRS (4 points) improved from baseline at day 14 with active drug.	SWM improved 19.8% over placebo at day 21. Spatial recognition, verbal fluency improved from baseline following active drug.
(Gallagher et al 2005)	Mifepristone	600 mg/day, 7 days	Double-blind, placebo controlled RCT	20	Schizo-phrenia (chronic, sympto-matic)	Stable for 6 weeks prior	No effect on BPRS or Calgary. Improvements in HDRS and MADRS in both arms of the study (nonspecific effect).	No effect

[a] These studies examined HPA axis responses only.

Abbreviations: BPRS, Brief Psychiatric Rating Scale; Calgary, Calgary Depression Scale; CGI, Clinical Global Impression; HDRS, Hamilton Depression Rating Scale; HPA, hypothalamic–pituitary–adrenal; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, Major Depressive Disorder; n/a, not assessed; RCT, randomized clinical trial; SWM, Spatial Working Memory (CANTAB); tid, three times daily.

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