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Mifepristone in Alzheimer's Disease

Vikas Dhikav*

Department of Neurology, PGIMER & Dr. RML Hospital, GGS-IP University, New Delhi, India

Corresponding Author:** ***Vikas Dhikav, *Department of Neurology, PGIMER & Dr. RML Hospital, GGS-IP University, New Delhi, India.* ***Email:*** *vikasdhikav@hotmail.com*

EDITORIAL

Alzheimer's disease is the most common cause of dementia worldwide and mifepristone is a pleomorphic drug with a potential to be tried in Alzheimer's disease[1].

The anti-progestational activity of mifepristone results from competitive blockade of progesterone receptors. Based on studies with various oral doses in several animal species, the compound inhibits the activity of endogenous or exogenous progesterone leading to the termination of pregnancy.

Mifepristone in doses of 1 mg/kg or greater have been shown to antagonize the endometrial and myometrial effects of progesterone in women. During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins and this action helps its abortifacient property.

The drug also exhibits antiglucocorticoid and in animals, it gets manifested in doses of 10 to 25 mg/kg. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats in high doses following repeated administration of doses from 10 to 100 mg/kg.

Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed with a peak plasma concentration occur within 1.5 hours of oral ingestion. The drug is 98% bound to plasma proteins, albumin and a $_1$-acid glycoprotein. The drug follows nonlinear kinetics and elimination of mifepristone is slow at first and rapid later with a terminal elimination half-life of 18 hours. The drug is eliminated mainly by faeces. Mifepristone undergoes N-demethylation and terminal hydroxylation of the 17-propynyl chain via CYP450 3A4.

Alzheimer's disease is frequently associated with abnormalities in the hypothalamic pituitary adrenal axis1. Elevated cortisol levels in Alzheimer's disease may in turn be associated with a more rapid progression of the illness. In addition, elevated cortisol levels may directly contribute to cognitive deficits in Alzheimer's disease. Mifepristone is a potent antagonist of the glucocorticoid receptor and blocks the central actions of cortisol2-3.

It has been assumed that subjects with high baseline cortisol levels experience greater declines in cognitive impairment over time relative to subjects with Alzheimer's disease who have low baseline cortisol levels[4]. The drug increases cortisol levels when given to those with Alzheimer's disease[5]. Glucocorticoid system has as a role of regulator of amyloid beta (Aβ) generation in patients with Alzheimer's disease highlighting the role of mifepristone[5].

Mifepristone was developed >30 years back by researchers at the French pharmaceutical company Roussel Uclaf. While investigating glucocorticoid receptor antagonists, investigators discovered that some of the compounds blocked the similarly shaped progesterone receptor. Refinement of the compound led to the production of RU486, the medication now known as mifepristone[6]. The drug has a good safety as indicated by a 1000 times normal dose of humans as lethal dose[6].

Mifepristone has a potential to be tried in the treatment of Alzheimer's disease based upon available evidence. However, dose, duration and potential adverse effects need to be worked upon in humans[7-9].

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