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Early onset of action of amineptine

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A priority in the treatment of depression is to obtain rapid improvement at an early stage. Since depressed patients, who are often convinced that nothing can be done for them, may well have difficulty in adhering to the therapeutic management plan, they can be both uncooperative and neglectful of treatment measures. The rapid correction of this often resigned apathy is an essential aspect of treatment. According to a variety of clinical criteria, amineptine often achieves rapid improvement, particularly on measures of psychomotor retardation. Initially, antidepressant medication is an essential measure in the relief of depressive symptoms, although subsequently, it may also become a complement to psychotherapeutic support. Amineptine has been shown to act directly on the dopaminergic pathway, unlike other antidepressants, which act on this system only via their effects on the serotonergic or noradrenergic systems.

Keywords: Amineptine, depression, early onset, mode of action, dopaminergic pathway

INTRODUCTION

Depression is a syndrome characterized primarily by a lowering of mood and by an inhibition of both mental and physical activities. It is a very common disorder: point-prevalence rates from community surveys in several countries have been in the range of 4.6–7.4% for major depression, while lifetime rates for the same disorder have been mostly in the range of 2.9–8.6%. Lifetime rates for dysthymia (chronic mild depression) are very similar: 2.2–4.7% (Smith and Weissman, 1992). Although the aetiology of depression remains uncertain, it is believed to have a multifactorial origin, involving genetic, biochemical, psychological and social causes, to varying degrees.

Psychopharmacological treatment of depression began in the late 1950s with the largely serendipitous discovery of the first antidepressants, imipramine (Kuhn, 1958) and iproniazid (Loomer *et al.,* 1958). Subsequently, the central neurochemical phenomena underlying the disorder have been continuously investigated, with a view to developing new and better psychotropic agents. The aim of these is to restore the neuropharmacological equilibrium, which is believed to have been disturbed in depression.

The majority of sufferers from clinical depression respond well to antidepressant drugs, but may need to be strongly encouraged to continue taking an adequate dose over a sufficient length of time. With most antidepressants, it takes 2–3 weeks before a therapeutic effect is experienced. During this time, patients are likely to experience some side effects, and may be tempted to stop the drug on the grounds that it is doing more harm than good. The risk of suicide may actually be somewhat higher during this time, and close supervision may be needed, particularly as some of the older drugs can be toxic in overdose. The maintenance of an active lifestyle, which is most desirable for recovery, requires both effective and well tolerated treatment. This may then avoid the need for admission to hospital, as well as allowing the continuation of work and social activities. It is therefore most desirable that antidepressants should have rapid effects upon both mood and psychomotor inhibition, and this efficacy then needs to be sustained (Allain *et al.*, 1995). Side effects such as sedation or dry mouth should be minimal, to help ensure good compliance.

Amineptine is a psychotropic agent that has been shown to have both psychostimulant and antidepressant properties. It has been suggested by a number of investigators that it has an earlier onset of action than other antidepressants (Van Amerongen, 1979; Deniker *et al.*, 1982; Delalleau, 1984; Ferro *et al.*, 1985; Dalery *et al.*, 1992).

MODE OF ACTION

Amineptine is a tricyclic drug with a novel chemical structure: it has a dibenzosuberan nucleus onto which a 7-aminoheptanoic chain has been grafted, and is thus an unusual antidepressant in terms of its mechanism and site of action. Amineptine is a selective inhibitor of dopamine reuptake and its effects are selectively exerted on the mesolimbocortical system, resulting in reactivation of this system (Deniker *et al.*, 1982).

Amineptine was found to be effective on pharmacological tests considered to predict antidepressant efficacy in humans. In particular, it antagonizes the despair behaviour of rodents (Porsolt's test, an animal model of antidepressant activity) and this effect is inhibited by dopaminergic antagonists (Borsini *et al.*, 1985), whether of D_1/D_2 (haloperidol) or D_2 (sulpiride).

Prolonged administration of amineptine also reduces the number of central β- and α_2-adrenergic receptors whereas, by contrast, it does not modify the number of 5-hydroxytryptamine $(5\text{-HT})_2$ receptors (Ceci *et al.*, 1986). In parallel with these findings, pharmacological studies have shown that amineptine does not exert any actions, central or peripheral, that might be indicative of clinical adverse effects. In particular, it is devoid of anticholinergic, sedative or cardiovascular effects (Setrakian, 1982).

Frontal cerebral structures have been attributed a major role in cognitive functions, particularly in the capacities for preparation, planning, prediction and anticipation of activities (Fuster, 1988). Moreover, both a negative distortion of present experience and the prevalence of unpleasant memories of the past can be interpreted as caused by impairment of dopaminergic innervation of the limbic system and prefrontal cortex (Stevens, 1979; Hervé and Tassin, 1986; Gaspar *et al.*, 1989). Many depressive illnesses are accompanied by decreased functioning of mesolimbocortical dopaminergic neurotransmission, assessed by assaying dopamine metabolites (Brozoski *et al.*, 1979). Activation of this system is an essential element of antidepressant activity. In the last decade, studies have shown that all serotoninergic or noradrenergic antidepressants eventually act on the mesolimbic dopaminergic pathway, after a variable delay and to varying degrees (Ollat, 1988). Amineptine is a dopaminergic antidepressant with direct and immediate effects on mesolimbocortical pathways (Mocaer, 1983).

Rapid restoration of the normal activity of these pathways is a primary objective of antidepressant treatment. There is a clear need to institute pharmacotherapy without delay, since clinical success may be influenced by the patient's experience during the early days of treatment. Furthermore, in the case of patients who are uncooperative, through being withdrawn and retarded, treatment must help restore their contact with reality and therefore should not be sedative.

The prolonged administration of antidepressants potentiates the motor response, mediated by the mesolimbic system, to dopaminergic agonists that are administered systemically. Prolonged administration of antidepressants also induces a greatly enhanced behavioural response on Porsolt's test, following injections of microdoses of dopamine into the nucleus accumbens (Plaznik and Kostowski, 1987). Repeated administration of desipramine induces hyperactivity of mesencephalic dopaminergic neurons (White and Wang, 1983). Finally, prolonged treatment with various antidepressants (imipramine, amitriptyline, iprindole, bupropion, citalopram, mianserin) both decreases the number of limbic D_1 receptors and increases the number of cortical D_1 receptors, without altering the number of mesolimbic D_2 receptors (Antkiewicz-Michaluk *et al.*, 1985; Klimer Vnielsen, 1987).

The D_1 dopaminergic receptors are heteroregulated via noradrenergic and serotonergic systems (Tassin *et al.*, 1982). Citalopram, for example, a selective inhibitor of serotonin reuptake, reduces the number of limbic D_1 receptors. Thus, antidepressants reduce the number and efficacy of limbic D_1 receptors via their noradrenergic/serotoninergic effects. This has two consequences: first, hyperactivity of presynaptic dopaminergic pathways arising from feedback mechanisms; and second, hypersensitivity of D_2 receptors (released from the negative interaction exerted by D_1 receptors on their stimulation). Consequently, all antidepressants increase dopaminergic transmission via limbic D_2 receptors.

A number of neurochemical, electrophysiological and behavioural studies have defined the effects of amineptine on mesolimbocortical pathways, especially its direct action on the dopaminergic pathways (Fuster, 1988). This mechanism distinguishes amineptine from the more conventional tricyclic derivatives, which principally inhibit noradrenaline reuptake; in addition, they may also inhibit serotonin reuptake (imipramine, clomipramine, amitriptyline, amoxapine). Its action is also distinguished from that of selective serotonin reuptake inhibitors (fluoxetine, citalopram, fluvoxamine, sertraline).

The possible effects of amineptine on locomotion are neutralized by inhibition of dopaminergic pathways, either by reserpine-induced dopamine depletion or by reduced neuronal activity caused by low-dose apomorphine, which stimulates dopaminergic autoreceptors (Chagraoui *et al.*, 1989). This indicates that the dopaminergic agonist effects of amineptine depend on the dopamine released by neuronal activity. Similar results have been obtained with CBR-12783, a dopamine reuptake inhibitor, but not with dexamphetamine, which stimulates dopamine release (Chagraoui *et al.*, 1989). Amineptine therefore acts as a selective inhibitor of dopamine reuptake.

Amineptine accelerates dopamine turnover within the limbic and nigrostriatal systems. Inhibition of reuptake of the dopamine released by presynaptic nerve endings leads to its metabolic breakdown, as indicated by the levels of its principal metabolite, homovanillic acid. Following administration of amineptine, homovanillic acid levels in the nucleus accumbens and striatum rise, while the levels of metabolites of other monoamines are not altered (Wald Meier, 1982).

Amineptine acts selectively on dopamine pathways originating in the ventral tegmental of the midbrain (area A_{10}), which project onto the limbic system and prefrontal cortex.

The activity of noradrenergic neurons of the locus coeruleus and serotoninergic neurons of the raphe nucleus are not modified by intravenous administration of amineptine. In contrast, the activity of dopaminergic neurons of the ventral tegmental area is markedly decreased, and this inhibition is antagonized by haloperidol (Scuvee-Moreau and Dresse, 1982). This effect can be explained by the fact that dopamine, which accumulates in the synaptic gap due to inhibition of its reuptake, exerts a more intense stimulation on presynaptic autoreceptors.

Study of the pharmacokinetics of amineptine reveals a number of important points from the therapeutic point of view. It is rapidly absorbed and eliminated, which allows a great flexibility in the dose: peak plasma concentrations are reached in approximately 1 h; the plasma half-life of amineptine and its principal metabolite are 1 and 2.5 h, respectively; the clearance rate is over 100 l/h. Furthermore, since the various pharmacokinetic parameters are not modified by prolonged drug administration, there is no risk of accumulation. Finally, the pharmacokinetic parameters of amineptine are not affected by age, although the elimination time of its principal metabolite is increased in the elderly, which justifies the use of lower doses in these patients (reviewed by Riché *et al.*, 1989).

EFFICACY AND EVIDENCE OF EARLY ONSET

Amineptine is thus an antidepressant with a mechanism and site of action which are unique in this class of drugs: its selective inhibition of dopamine reuptake specifically reactivates the mesolimbocortical stem. This mechanism of action largely accounts for its clinical properties: principally, rapid onset of action on psychomotor retardation, anxiety and insomnia (due to the direct and intermediate effects on the cerebral anticipation pathways), and ease of use (no noradrenergic or serotonergic activity and no sedative effect).

Controlled, double-blind studies have shown that the therapeutic efficacy of amineptine is at least equal and sometimes superior to that of the reference antidepressants with which it has been compared: clomipramine, imipramine, amitriptyline, fluoxetine, maprotiline and trimipramine (Van Amerongen, 1979; Lemoine *et al.*, 1980; Porot *et al.*, 1980; Ropert *et al.*, 1982; Oules and Boscredon, 1983; Carrier, 1987; Vauterin and Bazot, 1987; Dalery *et al.*, 1992). This efficacy has been shown in all the various subtypes of depression (Setrakian, 1982). Its longest effects on improvement in mood are complemented by those on mental and psychomotor activity. While the effects of amineptine are exerted on various aspects of the depressive syndrome such as depressed mood, anxiety, psychomotor retardation, and somatic disorders, the particularly rapid onset of beneficial effects on activity and psychomotor initiative allows the patient to resume social, work and family activities more rapidly. Amineptine is thus very useful in the rehabilitation of depressed patients. Its tolerability by patients is good, and generally better than that of reference drugs with which it has been compared. In particular, amineptine does not alter clinical and electrocardiographic cardiovascular parameters, does not have any sedative or anticholinergic effects (Setrakian, 1982) and can be coprescribed with other psychotropic drugs (with the exception of monoamine oxidase inhibitors).

The efficacy of amineptine in all types of depression has been demonstrated in a multicentre study (Deniker *et al.*, 1982), in which 1354 depressed patients were treated. Analysis of its antidepressant activity in a subgroup of 201 cases of endogenous depression, selected from the initial population, confirmed the drug's efficacy. This type of depression is associated with a high risk of suicide, and the absence of any suicide attempts in this subgroup appeared to confirm the safety of amineptine. Its rapid onset of action, significant by the seventh day or even earlier, and ease of use were also evident. Thus, although amineptine can be an antidepressant of choice in the routine treatment of neurotic depression, its efficacy has also been demonstrated in endogenous major depression, which is a less common disorder, but more difficult to treat. In another study (Petit and Setrakian, 1983) on the use of amineptine among 815 patients with reactive depression, the mean score on the Hamilton Rating Scale for Depression (HAMD) decreased from 18.6 to 10.9 (i.e. to 61% of baseline) by day 28.

In a double-blind controlled study in 51 patients suffering from moderate to severe depression, Van Amerongen (1979) found that amineptine at 200 mg/day produced an overall improvement in patients with neurotic, reactive or melancholic depression. This was similar to that obtained with 75 mg amitriptyline a day over a period of 6 weeks. Although there was no significant difference in the overall responses to the two drugs, differences were found in their effects on a number of items of the HAMD: amineptine showed a more rapid action than amitriptyline on items such as depressed mood and psychomotor retardation. Amineptine also differed from amitriptyline in that it was better tolerated overall and, in particular, did not produce any atropine-like side effects. However, the fixed dose of amitriptyline used in this drug trial was well below that required for a full therapeutic response in many cases.

Depression is almost always accompanied by sleep disorders with onset difficulties, frequent nocturnal waking and early morning waking. Polygraphic studies have also demonstrated that the depressed patient's sleep is characterized by a reduction in the onset time of rapid eye movement (REM) sleep, a reduction in the total duration of REM sleep and an increase in nocturnal waking times. However, amineptine preserves the sleeping–waking cycle and allows reorganization of the depressed patient's sleep. A placebo-

controlled study showed that 2 weeks of treatment with amineptine (200 mg/day) corrected the various sleep disorders of depressed patients: the time to onset was decreased, total sleep time increased and the number and duration of episodes of REM sleep increased (Di Perri *et al.,* 1987). This effect of amineptine had not previously been found with other antidepressants and may well be related to its beneficial effects on morning asthenia. It is therefore particularly useful both in elderly patients (Agnoli *et al.,* 1981) and in those who are still at work.

Ferro *et al.* (1985), in a study of 63 adults with mild to moderate depression, compared amineptine with both mianserin and amitriptyline. These authors found that the three antidepressants had similar therapeutic efficacy according to both overall clinical evaluation and objective tests. However, the group treated with amineptine responded more rapidly than the two others to treatment, and the clinical results from this point of view were confirmed by the tests performed. The scores of the HAMD item 'sexual symptoms' showed that the amineptine group resumed sexual activity in parallel with the improvement in depressive symptoms. This change, though, was not as evident in the mianserin group and even less so in the amitriptyline group. Amineptine did not trigger or aggravate the basic anxiety; indeed, a gradual and significant reduction in anxiety was detected, both after analysis of the data from the relevant item in the HAMD and according to the degree of muscle tension considered to reflect a state of anxiety. Although there was concomitant treatment with benzodiazepines, as is common in European antidepressant studies, this also occurred with the other two antidepressants, and the final results for anxiety showed no differences between the three groups. Overall tolerance was better in the amineptine group than in the mianserin group, where the most frequent side effects were apathy and daytime drowsiness; it was also better than in the amitriptyline group, where the initial sedative effects were later accompanied by frequent symptoms linked to the anticholinergic activity of this drug. The three antidepressants studied all showed clear therapeutic activity, and their specific effects were similar, but amineptine proved to be the best adapted to outpatient treatment because its therapeutic activity occurred more rapidly and it was better tolerated, particularly being devoid of any sedative effects. These properties should help to ensure better compliance and more rapid reintegration of the patient into active life.

Thus, a number of studies have demonstrated the rapid action of amineptine, especially on psychomotor retardation. For example, in the study by Deniker *et al.* (1982), 815 patients with reactive depression were significantly improved by the seventh day of treatment (34% reduction in HAMD score). The study by Dalery *et al.* (1992) also illustrated a rapid onset of action. This was undertaken in 169 patients suffering a major depressive episode (*Diagnostic and Statistical Manual of Mental Disorders*, DSM-III criterion), treated under double-blind conditions by amineptine (200 mg/day) or fluoxetine (20 mg/day). On the fourth day of treatment, an antidepressant effect was observed earlier with amineptine than with fluoxetine on four of the five rating scales (Clinical Global Impression, HAMD, the Montgomery–Åsberg Depression Rating Scale and the Widlöcher Scale); the significance of the changes in score on the scales were $P < 0.001$ for amineptine versus $P < 0.05$ for fluoxetine and results were identical for the fifth scale (Hopkin's Symptom Check-List). Of particular interest, the retardation item of the HAMD scale was significantly decreased in favour of amineptine ($P < 0.01$). After 3 months, the results demonstrated comparable antidepressant efficacy for the two drugs on the five rating scales used.

In this study, therefore, two selective inhibitors of neurotransmitter reuptake, dopamine for amineptine and serotonin for fluoxetine, differed in terms of the rapidity of their action, which is consistent with the theory of the final common pathway of antidepressant action discussed above. Because of the heteroregulation of receptors, an action on serotonin leads to an action on dopamine, resulting in modulation of mood. Amineptine directly and selectively activates dopaminergic pathways, and a direct action on these pathways may well mean a more rapid action.

CONCLUSIONS

Since depressed patients, who are often convinced that nothing can be done for them, may well have difficulty in adhering to the therapeutic management plan, they can be both uncooperative and neglectful of treatment measures. Rapid correction of this often resigned apathy therefore is an essential aspect of treatment. According to a variety of clinical criteria, amineptine often achieves rapid improvement, particularly on measures of psychomotor retardation. Initially, antidepressant medication is an essential measure in the relief of depressive symptoms, although subsequently, it may also become a complement to psychotherapeutic support.

Amineptine has been shown to act directly on the dopaminergic pathway, unlike other antidepressants, which act on this system only via their effects on the serotonergic or noradrenergic systems. The studies reviewed above contain much evidence to support the view that this effect accounts for amineptine's rapidity of action.

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