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M. Berger · M. Gastpar

Trimipramine: a challenge to current concepts on antidepressives

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Abstract Although it is chemically a classical tricyclic antidepressant agent, trimipramine shows atypical pharmacological properties. Its well-documented antidepressant action cannot be explained by noradrenaline or serotonin reuptake inhibition or by a down-regulation of β-adrenoceptors. Furthermore, its receptor affinity profile resembles more that of clozapine, a neuroleptic drug, than that of tricyclic antidepressants. Trimipramine does not reduce, but rather increases, rapid eye movement sleep. It stimulates nocturnal prolactin secretion and inhibits nocturnal cortisol secretion, and may act at the level of the hypothalamus on corticotropin-releasing hormone secretion. Trimipramine is of particular value in depressed patients with insomnia, and it has been shown to be effective in the therapy of primary insomnia. As the pharmacological profile indicates, and an open clinical study has shown, trimipramine might also be active as an antipsychotic. The drug is both a tool for increasing our understanding of depression and a potential therapy for several psychiatric disorders.

Key words Trimipramine · Dopamine receptors · Antidepressants · Primary insomnia · Schizophrenia

Introduction

Trimipramine, introduced to the market over 30 years ago as one of the first generation antidepressants, remains an atypical representative of this group of drugs. Whereas tricyclic antidepressant agents are thought to act through inhibition of neuronal uptake of noradrenaline (NA) and serotonin (5-HT), and through down-regulation of β-adrenoceptors, chronic administration of trimipramine is not associated with a down-regulation of β-adrenoceptors (Kopanski et al. 1983; Hauser et al. 1985). This probably explains why trimipramine, unlike other antidepressants, does not cause orthostatic hypotension in patients, even during intravenous therapy (Gastpar and Bauman 1987). Moreover, at therapeutic doses, trimipramine does not inhibit the synaptic reuptake of NA or 5-HT (Maitre et al. 1987; Cournoyer et al. 1987; Gross et al. 1991).

Clinically, trimipramine exhibits a similar side-effect profile to other classical antidepressants, but has minimal cardiovascular effects (Lapierre 1989; Cohn et al. 1993). While retaining the same efficacy in depressed patients as other tricyclic antidepressants, it has distinctive effects on sleep patterns in depressed patients.

Despite its long history of use, the mechanism of action of trimipramine remains unclear. However, recent studies have started to throw light on the unique clinical and pharmacological specificity of this drug. In providing an exception to the current dogma on the major mechanisms of antidepressive activity, trimipramine not only provides a tool to study the pathology of depression, but also offers potential for the treatment of nondepressive disorders.

This article highlights the recent progress in our understanding of the clinical and pharmacological activity of trimipramine and suggests new indications for its therapeutic use.

Depression and sleep patterns

Effects on REM sleep

The overwhelming majority of depressed patients experience sleep disturbances such as early-morning awakening. Rapid eye movement (REM) sleep occurs earlier than normal in depressed patients, leading to an icrease in the proportion of REM sleep (Rüther 1989; Berger and Rie-

M Berger
Klinikum der Albert-Ludwigs-Universität,
Universitätsklinik für Psychiatrie und Psychosomatik,
Hauptstrasse 5, D-79104 Freiburg, Germany

M. Gastpar
Klinik für Allgemeine Psychiatrie,
Rheinische Landes- und Hochschulklinik Essen,
Virchowstrasse 174, D-45147 Essen, Germany

mann 1993). Continuity of sleep is also disturbed. In fact, an increase in REM sleep, although not specific for primary depression, has been proposed as a diagnostic variable for depression (Rush et al. 1986).

This association between depression and REM sleep is also sustained in the clinical activity of the majority of antidepressive drugs. Irrespective of their proposed model(s) of action, antidepressants generally reduce REM sleep in parallel with their relief of depression (Berger 1987). This has been shown for tricyclic compounds such as amitryptyline and nortriptyline, tetracyclics such as mianserin, monoamine oxidase inhibitiors such as clorgyline and pargyline, and selective monoamine uptake inhibitors such as maprotiline, zimelidine, fluoxetine and indalpine (Nicholson and Pascoe 1989). Antidepressant efficacy, as a consequence, has been thought to be inevitably linked to inhibition of reuptake of noradrenaline and 5-hydroxytrypramine and to reduction of REM sleep. Trimipramine contradicts this widespread opinion, in that it does not have the typical effects on REM sleep architecture.

As shown in controlled clinical trials, trimipramine is at least as effective in the treatment of depression as imipramine, amitriptyline, doxepin, maprotiline, phenelzine and isocarboxazide (Settle and Ayd 1980; Lapierre 1989). In healthy volunteers and in animals, however, trimipramine had no effect on REM sleep parameters (Dunleavy et al. 1972; Khazan and Brown 1970; Chen 1979). Ware et al. (1985) also found that trimipramine failed to suppress REM sleep in depressive patients. This was confirmed in an open study in ten depressive patients by Wiegand and Berger (1989). After reaching a maintenance dose of 200 mg, patients were treated for a total of 3 weeks. The depression-specific changes in sleep pattern — in terms of time, efficiency and latency — improved, but REM sleep was not reduced. Under the treatment, even very short REM latencies (so-called sleep-onset REM periods) persisted, despite clinical improvement.

In a recent double-blind, comparative study, trimipramine was compared with imipramine in 20 male patients with major depression (Steiger et al. 1993). Following a 1-week washout period and a 4-day dose adjustment period, during which trimipramine was increased from 50 to 200 mg/day and imipramine from 50 to 150 mg/day patients received 200–250 mg/day trimipramine and 150–200 mg/day imipramine. Both treatments provided significant antidepressive responses (Hamilton score) within the first 2 weeks, without any significant differences between the two (Table 1). There were also no significant differences between the treatments with regard to subjective side effects. However, under trimipramine REM and deep sleep actually increased after 2 days, by which time imipramine was already decreasing both types of sleep. These effects were reflected in the influence of the treatments on sleep quality. These findings show clearly that antidepressive efficacy can be achieved without affecting amine transmitter uptake or compromising sleep. What then is the mechanism involved?

Table 1 Effects of 28 days treatment with trimipramine and imipramine on mean values for clinical state, sleep and nocturnal hormonal changes in patients with major depression (Steiger et al. 1993).REM rapid-eye movement; SWS slow-wave sleep

	Trimipramine ($n = 11$)		Imipramine ($n = 9$)	
	Day −1	Day 28	Day −1	Day 28
Hamilton score	29.3	10.7[a]	25.7	6.1[a]
Hormone concentrations (ng/ml) 23.00–07.00				
Cortisol	87.8	69.2[a]	86.6	83.2
Prolactin	9.8	15.1[a]	9.7	11.7
REM time (min)	66.5	81.2[a]	83.1	53.4[a]
SWS time (min)	21.8	37.8[a]	44.3	36.8

[a] Significantly different from day −1

Effects on circadian hormone responses

Normal sleep is associated with notable circadian changes in endocrine activity. In healthy humans plasma cortisol is low at the start of the night, rises abruptly to a first peak between 2 a. m. and 3 a. m., and has its maximum in the early morning. Growth hormone (GH) levels in plasma, on the other hand, reach a peak during the first few hours of sleep, falling to low levels during the second half of the night (Steiger et al. 1987). In depressed patients these neuroendocrinological variations are altered. Plasma cortisol levels reach a higher nocturnal maximum and exhibit a less pronounced and shorter fall during the middle of the night (Linkowski et al. 1987); the sleep-related growth hormone secretion is reduced (Voderholzer et al. 1993).

Studies with trimipramine (75 mg) given to healthy volunteers showed no effect of the drug on daytime plasma cortisol and GH, but a marked increase in plasma prolactin concentrations (Wiegand et al. 1986, 1987). This latter effect is reminiscent of the action of neuroleptic drugs and is commensurate with a dopamin blocking action of trimipramine. As in depressed patients, a similar increase in nocturnal prolactin secretion has also been observed by Wiegand and Berger (1989) in healthy volunteers treated with 75 mg trimipramine, suggesting that a hypothalamic-pituitary site of action of trimipramine may also exist for nondepressive conditions. In rats trimipramine only increased REM sleep in darkness, not in the light (Joanny et al. 1991), possibly reflecting an interaction with pineal function.

Steiger et al. (1989) confirmed the stimulatory effect of trimipramine (200 mg/day) on nocturnal prolactin secretion and lack of effect on GH in healthy volunteers, but also found that trimipramine inhibited nocturnal cortisol secretion and delayed the early-morning rise in cortisol secretion.

In the double-blind comparative trial of trimipramine and imipramine, described above, only trimipramine, and not imipramine, decreased nocturnal cortisol and increased nocturnal prolactin (Table 1) in parallel with the

improvements in Hamilton score and REM and slow-wave sleep (Steiger et al. 1993). Imipramine and other antidepressants, if anything, tend to enhance nocturnal cortisol secretion.

Since patients with affective disorders have an elevated nocturnal cortisol secretion, its inhibition by trimipramine might directly influence the pathophysiology of depression. This is underlined by the finding that under treatment of depressed patients with trimipramine (200 mg/day) for 6 weeks, the previously elevated cortisol response in the combined dexamethasone–human-corticotropin-releasing hormone stimulation test is normalized (Holsboer-Trachsler et al. 1991, 1994).

Effects on dreams

In addition to the beneficial maintenance or improvement of the extent of REM sleep in depressed patients under trimipramine therapy, dreams are also influenced positively. In an investigation of dream recall and content in 1707 depressive outpatients, Riemann et al. (1990) found that antidepressant treatment with trimipramine (200 mg/day for 4 weeks) led in parallel to relief of depression and sleep disturbances, to a marked increase in patients' rating of dreams as pleasant. This result, however, is limited by the low rate of dream recall in the examined patients and by the open design of the study.

Effect of combination with adjunct therapies

Under antidepressant therapy, the onset of measurable clinical improvement regularly occurs up to 2 weeks after the initiation of therapy. In animal studies the delay in onset of action of almost all antidepressants is associated with an up-regulation of dopamine receptors, particularly in the nucleus accumbens (Fibiger 1995). Several studies have suggested that adjunct therapy with total or partial sleep deprivation hastens the onset of clinical drug action (Leibenluft and Wehr 1992). Seifritz et al. (1993) tested the combination of trimipramine (200 mg/day) with or without partial sleep deprivation in a randomized parallel group trial in 18 patients with major depression. They found that the adjunct treatment led to an improvement of polysomnographic and subjective sleep parameters (including sleep latency, waking time and deep sleep) suggesting that this treatment method may be indicated for the therapy of depressive insomnia.

The results of a single photon emission computed tomography (SPECT) study and an investigation of the eye-blink rate in depressed patients indicate that sleep deprivation, like amphetamine administration, leads to increased dopamine release in the limbic system (Ebert et al. 1994, 1995). It thus seems likely that trimipramine and partial sleep depriviation may be of benefit in depressed patients through interactions at the level of dopamine neurotransmission.

Therapy of primary insomnia

Antidepressants with sedative properties may be considered the drugs of choice in depressed patients suffering from secondary insomnia (Wiegand et al. 1986). They are also major candidates for the treatment of primary insomnia. In view of the sleep-promoting properties of trimipramine, Hohagen et al. (1994) performed a single-blind study with trimipramine (50–200 mg/day) for 28 days on 15 middle-aged patients suffering from primary insomnia (according to DSM-111-R) who had been taking benzodiazepines continuously or discontinuously for up to 5 years. The treatment with trimipramine produced a significant increase in sleep efficiency, total sleep time and a significant decrease in waking time. The patients reported an improvement in subjectively perceived sleep quality and in well being during the daytime. Sleep measurements 4 and 14 days after treatment discontinuation demonstrated that drug withdrawal did not provoke either short- or long-term rebound insomnia in the subjective evaluation of sleep. The objective measurements revealed that a subgroup of patients displayed total sleep time which was below baseline values during short- and long-term withdrawal of trimipramine, but generally without a concomitant worsening of the subjectively perceived sleep quality.

These findings suggest that trimipramine may be an effective alternative to benzodiazepines, for which the phenomenon of rebound insomnia is a substantial problem in the therapy of primary insomnia and can last for several weeks after withdrawal of the drug (Gillin et al. 1989). The possible advantage of trimipramine over benzodiazepines in this regard in the therapy of primary insomnia has yet to be demonstrated in randomized double-blind studies. The anticholinergic side effects and the necessity for stepwise increase in dose of trimipramine must be set against the addictive potential of the benzodiazepines.

Therapy of schizophrenia

The use of antipsychotic drugs is limited by their common extrapyramidal side effects. Atypical neuroleptics, such as clozapine, are characterized by a lower frequency of extra pyramidal side effects. Antipsychotic efficacy of neuroleptics is correlated generally with affinity for dopamine D_2 receptors (Seeman 1992). For over a decade trimipramine has been known to differ from other tricyclic antidepressant drugs in its ability to bind to DA receptors having a higher affinity for D_2 than for D_1 receptors (Carlsson and Lindqvist 1978; Waldmeier 1982; Richelson and Nelson 1984; Gross et al. 1991). As for neuroleptics, an action on D_2 receptors has been suggested to underlie an assumed antipsychotic effect of trimipramine (Seeman 1992). Interestingly, radioligand binding studies (Gross et al. 1991) show that the affinities of trimipramine for DA receptors, α_1-adrenoceptors and 5-HT_2 receptors closely resemble the values obtained for the atypical neuroleptic drug clozapine (Table 2).

Table 2 Comparative receptor binding affinities of D, L trimipramine and clozapine (after Gross et al. 1991)

Receptor	pK_i (nM)	
	Trimipramine	Clozapine
5-HT_2	7.71	7.84
$\alpha_{1A/B}$	7.62	8.54
D_2	7.24	7.01
D_1	6.46	6.58
α_{2B}	6.42	7.08
5-HT_{1C}	6.27	8.40
α_{2A}	5.86	7.10
5-HT_3	5.04	7.00
5-HT_{1A}	< 5.00	6.17
5-HT_{1D}	< 5.00	5.68

The cloning of DA receptors has recently revealed further subtypes in this receptor family. The D_2-receptor group is now known to consist of three subtypes: D_2, D_3 and D_4. Whereas the D_2 receptor remains the main target for most neuroleptic agents (Seeman 1992), clozapine is atypical in that it has a low property to produce extrapyramidal side effects and is more selective for the D_4 receptor (Van Tol et al. 1991). The dissociation constants for trimipramine have been measured recently at the D_4 receptor (257 nM) and the D_2 receptor (143 nM), and suggest that therapeutic doses of trimipramine will occupy both receptor subtypes (P. Seeman, pers. commun.). Because the atypical neuroleptic action of clozapine is thought to be based on its affinity for DA D_4 receptors, these findings with trimipramine underline its potential efficacy as an atypical neuroleptic agent.

Based on the similarity between the receptor pharmacology of clozapine and trimipramine, and the fact that both cause an increase in nocturnal prolactin secretion (Wiegand and Berger 1989), Eikmeier et al. (1991) studied the antipsychotic action of trimipramine (100–400 mg/day for 35 days) in 28 patients in the acute phase of schizophrenia as assessed by Brief Psychiatric Rating Scale (BPRS) and CGI. Significant improvements in total BPRS scores and in the subscores anxiety/depression, apathy and thought disturbance were obtained. Of the 28 patients, 13 (46%) improved to such an extent under the treatment with trimipramine that they were discharged from hospital on trimipramine maintenance therapy. This response is markedly higher than that which might be expected under placebo or that which may be caused by hospital admission alone. Therefore, an antipsychotic action of trimipramine seems likely. On the other hand, 6 patients had to be withdrawn from the study during the first week because of deterioration, and 9 patients showed either insufficient improvement or worsened again after an initial improvement. No clinically relevant extra-pyramidal symptoms occurred under the treatment.

Conclusions

Despite the fact that trimipramine does not inhibit NA or 5-HT reuptake, as do other tricyclic antidepressant agents, it is effective in major depression. The lack of inhibition of amine transmitter reuptake may explain the fact that trimipramine has no suppressing effect on REM sleep. In view of its sleep-promoting properties, trimipramine is the drug of choice for depressive patients suffering from insomnia. In addition, trimipramine offers an alternative to benzodiazepines in the treatment of primary insomnia because it does not cause a signficant rebound insomnia on withdrawal. The association of changes in sleep with changes in plasma cortisol and prolactin suggest that the hypothalamus–pituitary axis, and CRH in particular, may represent a major site of action of trimipramine. An action at the level of dopamine neurotransmission also seems likely.

The similarity between trimipramine and the atypical neuroleptic clozapine, both with regard to dopamine receptor affinities and lack of extra-pyramidal side effects, suggests that trimipramine may also have a place in the therapy of schizophrenia.

The profile of trimipramine clearly challenges current thinking about antidepressants, and although well tried, may still open new avenues for both therapy and understanding of pathophysiology.

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