Trimipramine, Anxiety, Depression and Sleep

J.C. Pecknold and L. Luthe
Douglas Research Center, Quebec, Canada

Summary

The presence of mixed symptoms of anxiety and depression are well known to every clinician. Panic, generalised anxiety and obsessive-compulsive disorder all have considerable overlap with major depressive illness. Factor analysis of anxiety and depression symptoms has sought to predict response to treatment as well as to establish a diagnosis. Sleep disturbances are important concomitants of both syndromes. The analysis of the architecture and phasing of sleep stages has been proposed as a biological marker to separate anxiety and depression. The modification of REM and delta sleep has been correlated with antidepressant action.

The earliest studies of trimipramine noted antidepressant, anxiolytic and hypnotic effects. Further observations have shown this drug to have atypical effects on REM sleep. In addition, despite its structural similarity to other tricyclic antidepressants, its pharmacological profile in animals is very different: there is no synaptosomal reuptake of serotonin or noradrenaline, and no desensitisation of \( \beta \)-adrenoceptors after long term administration.

A series of studies was carried out on 99 patients. Admission criteria for the studies specified a minimum score of 20 on the Anxiety Status Inventory as well as the presence of moderate depression. An uncontrolled trial demonstrated the anxiolytic efficacy of trimipramine. Further controlled trials showed superior anxiolytic efficacy of trimipramine to amitriptyline and doxepin with comparable anxiolytic efficacy of trimipramine with maprotiline. All agents had equal antidepressant effects.

In the earliest trials of trimipramine (Lambert et al. 1961; Sigwald et al. 1956) improvement in 70% of neurotic states was subsequently confirmed in depressive states (Juillet et al. 1962; Vidal et al. 1962). These early studies noted the antidepressant, sedative and tranquillising actions of this drug. In 1964 Rouleau recorded that one of the most important effects of the drug was decreased anxiety especially in depressive neurosis and involutional melancholia. Erutka et al. (1964) noted a significant reduction in anxiety and improvement in sleep from the second week of treatment. The initial findings of these trials called for controlled studies to investigate the efficacy of trimipramine in anxiety-depression, particularly in comparison with other antidepressant agents.

Anxiety and depression are closely associated dysphorias (Lehmann 1983) and can coexist in a number of ways, e.g. a secondary depression in an anxiety disorder like panic or obsessive-compulsive disorder or a variant of atypical depressions. Of patients with primary depression, 60% also have a diagnosis of an anxiety disorder (Fawcett & Kravits 1983; Leckman et al. 1983) and, conversely, 44% of patients with anxiety neurosis report episodes of depression (Clancy et al. 1978).
This percentage may be even higher in chronic states of anxiety such as agoraphobia. A number of attempts, including the early Newcastle-London confrontations (Klerman 1985), have been made to discriminate between anxiety and depression based on syndromal characteristics. More recently, Andreassen et al. (1986) demonstrated that the Newcastle Scale, which discriminates against anxiety symptoms in endogenous depression, was more sensitive than DSM III, RDC or Yale in detecting the familial transmission of recurrent unipolar depression. Extending such work, several neurochemical studies have discriminated between anxiety and depressive disorders with the DST and platelet imipramine binding (Pecknold in press). Using polysomnographic methods, Akiskal (1984) showed a shortened REM latency and an increased REM percentage in dysthymic disorders compared with anxiety depression. Dubé et al. (1984) separated primary affective disorders from anxiety states on the basis of the Arecholine Challenge Test which produced shortened REM latency in depression but not in anxiety.

Response to treatment constitutes the major concern for the clinician. Initial findings from the Newcastle group revealed that patients with neurotic depression associated with high levels of anxiety responded poorly to ECT and less well to imipramine than did those with endogenous depression (Carney et al. 1965; Kiloh & Garside 1963; Roth et al. 1972). The London St Thomas’ Hospital group (Sargent 1960; West & Dally 1959) and others (Liebowitz et al. 1984) found that in atypical depression with high levels of anxiety, a more successful outcome emerged with monoamine oxidase inhibitors (MAOIs) than with ECT or imipramine. Overall et al. (1966) found that anxious-tense patients responded more effectively to thioridazine than imipramine. At present, in the tricyclic antidepressant (TCA) group, trimipramine, doxepin, maprotiline and amitriptyline, all sedative agents, are recommended for the treatment of depressed patients with severe anxiety and sleep disturbance.

To ascertain the efficacy of these various agents in depression with important anxiety, several studies were carried out in Canada by Pecknold et al. (1978, 1979, 1985) and by Assalian et al. (1985).

1. Methodology

Three studies in 99 depressed outpatients with important anxiety and a minimum score of 20 on the Anxiety Status Inventory (ASI) [Zung 1975] were carried out. All studies had a mandatory 1-week placebo washout after which, in the first study, which was uncontrolled, patients received trimipramine for 6 weeks; in the second study patients received, in a double-blind fashion, either trimipramine or amitriptyline, and in the third study, also double-blind, either trimipramine or maprotiline.

1.1 Diagnostic Criteria

All patients were considered to have a well-established endogenous depression which was not bipolar in type and was at least moderate in severity. Re-evaluation of patient records indicates that the current diagnostic label of major depressive disorder on DSM III criteria would have been applicable to these patient groups in the earliest protocols in an uncontrolled study of trimipramine and a controlled comparison study of trimipramine and amitriptyline.

In the first uncontrolled study with 30 patients, although the minimum Hamilton Depression Rating Scale (HDRS) [Hamilton 1960] criterion was 14, at entrance patients had an HDRS average total score of 32.7 and patients were rated on the Clinical Global Impression (CGI) Scale as moderately ill (17 patients), markedly ill (12 patients) and severely ill (1 patient).

In the second study, a comparison between trimipramine and amitriptyline, 30 patients were selected. Despite the minimum criterion of 14 on the HDRS, these patients at entrance averaged 32.6 ± 1.9 and were considered to have a moderate to severe depression on the CGI Scale.

In the third study of trimipramine and maprotiline in 39 patients, all patients had unipolar major depression according to DSM III and RDC cri-