Effects of Zimeldine, Mianserin and Amitriptyline on Psychomotor Skills and their Interaction with Ethanol
A Placebo Controlled Cross-Over Study

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Summary. 13 healthy volunteers participated in a double-blind, four-period, cross-over study. In each period, the trial drugs (placebo, zimeldine, amitriptyline and mianserin) were given in fixed dosages for 8 days; amitriptyline 10–50 mg twice daily, mianserin 10–30 mg twice daily and zimeldine 200 mg once daily. Ethanol 1 g/kg bodyweight was drunk 2 hours after drug intake on Days 1 and 8 of each period, the latter being separated by a 2 week wash-out period. Ratings of subjective feelings and side effects, and performance tests were done on Days 1 and 8 of each period before, 1.5, 3 and 4.5 h after drug intake, i.e. 2 of the tests were performed under the influence of ethanol. Mianserin decreased critical flicker frequency, slowed reactions under discriminative stimulation and tended to cause nystagmus, but only on Day 1 (after the first 10 mg dose). Amitriptyline impaired coordination on Days 1 (after the initial 10 mg dose) and 8, and lowered the flicker threshold on Day 8 at “steady state” (after the 50 mg morning dose). Both these antidepressants were felt to be sedative, especially in the initial phase of the treatment, and they interacted additively with ethanol. Mianserin decreased critical flicker frequency, slowed reactions under discriminative stimulation and tended to cause nystagmus, but only on Day 1 (after the first 10 mg dose). Amitriptyline impaired coordination on Days 1 (after the initial 10 mg dose) and 8, and lowered the flicker threshold on Day 8 at “steady state” (after the 50 mg morning dose). Both these antidepressants were felt to be sedative, especially in the initial phase of the treatment, and they interacted additively with ethanol. No impairment of psychomotor skills was associated with zimeldine, only a subjective sedative effect of the 200 mg dose was seen on Day 1. Zimeldine did not enhance the effects of ethanol; it even showed some antagonism of ethanol-induced body sway in the standing steadiness test. In contrast to amitriptyline and mianserin, zimeldine was regarded as not harming psychomotor skills, and as not having any observable interaction with ethanol.

Key words: zimeldine, amitriptyline, mianserin; alcohol interaction, coordination tests, critical flicker fusion, body sway, psychomotor skills, tolerance

The clinical importance of antidepressant-ethanol interaction in high doses is apparent in view of the large number of reports of poisoning due to this combination. At recommended doses and ‘accepted’ alcohol concentrations, impaired driving ability and increased accident potential must be considered (Seppälä et al., 1979).

Zimeldine is a recently developed, selective 5-HT reuptake inhibitor (Ross and Renyi 1977; Ögren et al. 1981 b), which has shown marked antidepressant potency, low frequency of side effects and no sedative effects in clinical trials (Loudon et al. 1981; Coppin et al. 1979; Swift et al. 1981). After oral intake, zimeldine reaches its peak plasma concentration within 1–2 h and norzimeldine within 4–8 h (Love et al. 1981; Holmberg 1981). In a preliminary report, zimeldine alone did not affect psychomotor skills and cognitive function in normal volunteers (Ferris et al. 1981).

According to animal experiments, no pharmacokinetic or pharmacodynamic interaction with ethanol has been shown by zimeldine (Cott and Ögren 1980; Ögren et al. 1981 a, b). However, attenuation of ethanol consumption has been reported to follow treatment with zimeldine of ethanol-prefering rats in a free choice situation (Rockman et al. 1979 a, b, 1982). The absence of pharmacodynamic interactions between ethanol and zimeldine might be attributed to the weak histaminergic-(H1)-blocking potency of the compound (Cott and Ögren 1980). An earlier human study, measuring body balance with the Wright Ataximeter, suggested a lack of interaction between zimeldine and ethanol (Scott et al. 1982).

The purpose of the study was to examine the interaction between zimeldine and ethanol by using a wide range of tests. Zimeldine was compared with placebo and two other antidepressants, mianserin and amitriptyline, which are known to have an additive interaction with ethanol in man (Landauer et al. 1969; Seppälä et al. 1975; Seppälä 1977; Wilson and Ban 1982), and which clearly show a greater effect of this combination in animal studies (Cott and Ögren 1980). Since tolerance to the sedative effects of an-
tidepressants may develop, psychopharmacological evaluation was made both in the initial phase of the treatment and after one week of treatment with the various drugs.

**Material and Methods**

**Subjects**

Thirteen healthy volunteers (5 men, 8 women) of normal weight, aged 20–24 years, were included in the study. They were informed about the nature of the trial and their written consent was obtained. They were ascertained to be healthy by complete clinical examination, ECG and a set of laboratory tests, consisting of total blood picture, S-ASAT, S-ALAT, S-γGT, S-alkaline phosphatase, S-bilirubin, S-LDH, S-cholesterol, S-triglycerides and urinalysis. Laboratory tests were repeated after each treatment period. On session days the subjects were not allowed to drive motor vehicles and, whenever necessary, were transported by taxi.

Volunteers with a regular alcohol intake or drug abuse were excluded, as were those with acute or chronic illness, and any who had taken drugs of any kind likely to interfere with the treatment during the previous month. Lactating and pregnant women, as well as women who could not exclude the possibility of becoming pregnant during the study period, were also excluded. Subjects with previous hypersensitivity reactions to psychotropic drugs, and subjects who were not willing to give up alcohol, drinking or driving during the study were excluded.

**Treatment**

The subjects received zimeldine (Zelmid, Astra Läkemedel, Sweden), mianserin (Tolvon, Organon, The Netherlands), amitriptyline (Tryptizol, Merck Sharp & Dohme, USA) or placebo in random order for periods of 8 days, according to a double-blind, cross-over design. A 2-week wash-out period separated the treatment periods. The doses given are presented in Table 1. For reasons of uniformity the tablets were encapsulated, and were given in dose-packed tablet blisters (APO-DOS®).

**Ethanol**

Ethanol was given as an alcoholic bitter (Carillo, Chymos, Finland), mixed with water to yield a 17% (w/w) ethanol solution. The ethanol dose was 1 g/kg body-weight. Drinking time was 40 min.

**Trial Design**

To minimize interference between the effects of treatment and that of training, all subjects underwent a thorough training period before the study.

During treatment the subjects were tested in 8 sessions, twice during each treatment period; the time scheme used during each period is shown in Table 2. The subjects fasted overnight and during the test sessions. The tests were performed before and at fixed intervals after drug and ethanol administration. The trial design made it possible to compare both the effects of the antidepressants alone after 1.5 h and their interaction with ethanol after the first dose (on Day 1) and during “steady-state” after 1 week of treatment. To check compliance by the subjects, plasma samples were collected on Days 3, 6 and 8 of each period for analysis of the plasma antidepressant concentration.

**Assessments**

**Subjective Assessments.** Subjective feelings were measured, 4 times during every session, before, after drug intake and twice after subsequent ethanol intake. A questionnaire was used in which the subject had first to answer the question: “What kind of drug do you think you have received, a tranquilizer or a placebo?” Further ratings included feelings of performance, state of inebriation, alertness, clearheadedness, relaxation and happiness, by means of 100 mm visual scales. Eight side effects were also specifically asked about in the questionnaire. On each session day before drug intake, spontaneously reported adverse symptoms during the previous week were recorded by the investigator, before active questioning according to a questionnaire.

**Objective Tests**

The binocular flicker fusion test was done using a light-emitting diode. Critical flicker fusion frequency (CFF) was recorded at a distance of 100 cm from the flickering red light (Ø 3 mm, light to dark ratio = 10% light time), using the ascending method (Seppälä et al. 1980). Pupil constrictors were used.

Coordination of both hands was measured for 20–22 s with a Wiener Koordinationsgerät (Linnoila and Mattila, 1973). Both the number of deviations from the track and the mistake % were recorded.

Simple and choice reactions were measured with an apparatus utilizing 3 different light stimuli and