DOUBLE-BLIND STUDY OF THE EFFECTS OF
A COMBINATION OF BROMAZEPAM-ALCOHOL
VS PLACEBO-ALCOHOL IN 11 AUTOMOBILE DRIVERS

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SUMMARY : The potential reciprocity between alcohol drinking and benzodiazepines is frequently evoked in traffic safety. The aim of this double-blind cross-over study on 11 healthy drivers is to know eventual related effects of oral bromazepam (6 mg/day) with alcohol drinking (0.5 g/l).

The study is divided in 4 periods of 7 days (treatment or placebo) each separated to the next one by a 7 days wash-out. The tests are performed at the end of each period without or with alcohol drinking, just before.

Tests performed study different parameters of vigilancy, and performances in real driving situation.

For such a design the results show no significant differences between placebo-alcohol group and bromazepam-alcohol group.

The reciprocal potentialization associated with simultaneous intake of alcohol and Benzodiazepines is a problem which is frequently raised in relation to road safety.

This notion is primarily based on "a posteriori" studies of road accidents and in most cases an over intake of one or other of the products is observed. Without, in any way, putting into question the principle of a potentialization, frequently studied elsewhere, it seems of interest to us to study this problem from the standpoint of the general practitioner. Patients treated with anxiolytics sometimes ask if they can drink moderate amounts of alcohol.

We concerned ourselves specifically with the combination of a non-sedative anxiolytic treatment, Bromazepam, and a mean alcoholemia level which, while legal in France, is illegal in other countries of the EEC. This level was fixed at between 0.4 and 0.5 g/l.

Bromazepam is an anxiolytic benzodiazepine which bioavailability is 84 %. T max is about 1h 30 and elimination half-life is 20 hours.

Bromazepam has broadly an urinary elimination by the way of inactives metabolites.

This double-blind placebo-controlled study with cross-over was carried out in 11 healthy male volunteers, aged between 18 and 32 years with no progressive disease and no other drug intake during the time of experimentation. The only
allowable intake of alcohol during the study was that required for the carrying out of test for each subject.

Methods:

Four test sessions took place:

- at D7 after 7 days of treatment with placebo or Bromazepam (study of product effect only)
- at D21 after 7 day wash out and 7 days of bromazepam or placebo (study of product effect only)
- at D35 after 7 day wash out and 7 days of treatment (placebo or Bromazepam) with a single intake of alcohol prior to test session
- at D49 After 7 day wash out and 7 days of treatment (Bromazepam or placebo) and a single intake of alcohol prior to test session.

Two cross-overs were thus carried out:

  - between D0 and D21
  - between D28 and D49

The two cross-overs were independent one from the other and the sequence placebo-active product was not necessarily the same for each subject.

Alcoholemia measurements were taken at D35 and D49 using a breathalyser. Tests for the presence of Benzodiazepine in urine were carried out at D7, D21, D35 and D49.

The experimental protocol was submitted to and approved by the institutional review board of Grenoble. Informed consent was obtained from subjects prior to the beginning of the study.

Appendix 1

The test battery carried out at each session consisted of:
  - a self-appraisal questionnaire concerning
    - internal tension
    - level of anxiety
    - degree of drowsiness
    - psycho-retardation
    - physical retardation
  - a test of diffused attention
  - a study of emotional control of muscular tone (measurement of the polygon of support)
  - a driving test carried out in real traffic conditions with a simultaneous study of visual reaction times to stimuli appearing in different places in the field of vision, as well as a study of reaction time to auditory stimuli.

The analysis of results was carried out in 2 stages:
a curve was plotted for each test for each subject: on the abscissa, the chronological order of test taking, and on the ordinate the subject score, the higher the value the worse the score.

This non-statistical method permitted a first approach to the effects of different treatments with the appearance of "troughs" corresponding to improvements, and peaks corresponding to deteriorations.

This procedure, complementary to conventional statistical analysis, allows by a descriptive approach the detection of subjects who are particularly sensitive or resistant to the effects of treatment.

The strictly statistical analysis consisted of:

- a one factor (time) analysis of variance of the 4 test sessions by chronological order
- an analysis of the effect of alcohol alone, whether the subject received Bromazepam or not (Wilcoxon test)
- an analysis of the effect of the treatment product, whether the subject took alcohol or not (Wilcoxon test)
- separate analysis of the two cross-overs: order effect, treatment product effect (Wilcoxon test)

Results
On a statistical level, the study reveals no significant differences, for the different tests, between the placebo group and the Bromazepam group, when there is no association with alcohol. This study, correlated to other studies carried out with Bromazepam, confirms the absence of a sedative effect at usual therapeutic doses (6 mg/day)

A previously recognized notion however appears: a sensation of drowsiness is observed in certain subjects, but it is not associated with a decrease in performance contrary to what has been observed with an isolated intake of alcohol.

Moreover, no significant difference has been found between the placebo-alcohol group and the Bromazepam-alcohol group.

These results thus allow it to be stated that the classical alteration of performance associated with alcohol intake and proportional to the amount ingested are in no way potentialized by a moderate therapeutic dose of Bromazepam.

Comparison with the data in the literature however indicate that there is a summative effect, more than potentialization, when the dose of Bromazepam is higher than 12 mg/day and the alcoholemia level is greater than 0.8 g/1.

Conclusion
It is advisable to draw to the attention of patients treated with Bromazepam the danger of an alteration of performance and vigilance when the product is combined with alcohol. Above a certain threshold the two products together lead to an alteration of performance.
Nevertheless, it can be stated that with usual doses of Bromazepam the performance level is linked to alcoholemia and is not potentialized by the treatment.

The alcoholemia must, of course, be as close to zero as possible in patients under treatment as well as in those not under treatment.

BIBLIOGRAPHY


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