KINETIC INTERACTION OF NOMIFENSINE WITH A 1, 5-BENZODIAZEPINE (CLOBAZAM)

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1 Among the numerous possibilities of drug interactions, pharmacokinetic interactions may cause mutual changes in absorption, distribution, metabolism and elimination of either drug. In the present study this approach was used to investigate pertinent effects of nomifensine and clobazam.

2 Ten normal subjects participated in an intra-individual comparison of nomifensine 75 mg alone and in combination with clobazam 15 and 30 mg. The study design was carried out according to a Latin square in double-blind conditions. One-week wash-out periods were used between the trial days. Serum levels of nomifensine were measured by radioimmunoassay (RIA) and of original clobazam by gas chromatography (GC). Classical criteria for bioavailability (peak serum levels, time of peak, area under the serum level time curve) and the half-time of elimination from the serum were used for retrieval of pharmacokinetic information.

3 Results showed no relevant differences in the criteria mentioned above, after administration of each drug alone or in combination. Therefore, extrapolations were made to multiple dose kinetics based on assumptions derived from practical therapy. They showed comprehensive agreement with therapeutic results in depressed patients.

4 The use of the classical criteria for bioavailability, in addition to the calculation of the half-time of elimination from serum, provides sufficient information for the decision whether pharmacokinetic drug interaction is present or absent. There was no such interaction after single doses of nomifensine or clobazam.

Introduction

There are numerous possibilities of drug interactions from physicochemical reactions during mixing *in vitro* to competition at receptor sites in the body of the treated patient. We will concentrate on the pharmacokinetic interactions, which are related to the effect of one drug on the absorption, distribution, metabolism or excretion of another drug, as defined by Prescott (1969). Changes in the duration and intensity of action of a drug can be altered by another (Rowland & Matin, 1973; Kosman, 1974; Braithwaite, 1976).

For practical reasons the antidepressant, nomifensine, was variably combined with the new anxiolytic, clobazam, an unique 1,5-benzodiazepine compound.

The clinical pharmacologist was asked accordingly to answer the questions implied by the title of this contribution (Rupp, 1974).

Study design and methods

Ten normal male subjects (aged 26–51 yr, height 172–184 cm, weight 61.5–95.5 kg) from the permanently supervised panel of volunteers maintained by our Clinical Pharmacology Unit, participated in the study after giving informed written consent. The design was an intra-individual comparison of nomifensine 75 mg alone and in combination with clobazam 15 and 30 mg, using a Latin square randomization in double-blind conditions. The medication was given with a standard breakfast to all subjects on the same day. There was a wash-out period of one week between trial days. Blood samples were taken from a cubital vein before medication and 60, 140, 270, 350 min and 24 h after medication. Serum concentrations of nomifensine were measured by RIA (Heptner *et al.*, 1977), and original clobazam by GC (Hajdú & Uihlein, 1977).

The classical criteria for bioavailability—that is,

Figure 1 Peak serum levels of original clobazam (GC) and nomifensine (RIA) after sole and combined medication. Mean $\pm$ s.e. of ten subjects. Latin square design.

Figure 3 Areas under the serum level curves.

Figure 2 Times of peak serum levels of original clobazam (GC) and nomifensine (RIA) after sole and combined medication.

Figure 4 Half-times for elimination from serum of original clobazam (GC) and nomifensine (RIA).

peak serum concentration, time of peak, and area under the serum concentration-time curve—were calculated following the recommendations of the World Health Organization (1974).

The pharmacodynamic effects measured in this study, using a battery of psychological tests, will be published elsewhere (Koeppen *et al.*, 1976).

Results

The results of the study are presented in simple figures arranged in a similar way. The column on the right-hand side shows the means of the respective variable

Figure 5 Extrapolated multiple dose kinetics of nomifensine and clobazam.

for nomifensine 75 mg alone. The column on the left represents the means for clobazam 30 mg. In between, there are the results of the combinations clobazam 30 mg plus nomifensine 75 mg, and for clobazam 15 mg plus nomifensine 75 mg.

Figure 1 shows peak serum concentrations of nomifensine and original clobazam. There is no significant difference between the single components and the combinations. The same is true for the times of peak serum levels presented in Figure 2.

The third classical criterion for bioavailability are the areas under the serum concentration—time curves, shown in Figure 3. Again, there is no difference between the single components and the combination.

Summarizing our results, it may be concluded that there is no relevant mutual interactions between nomifensine and clobazam on absorption and distribution of either drug.

There could be, however, interaction at other steps in the pharmacokinetic process. Shifts in protein binding or competitive inhibition of renal excretion would be indicated by significant differences in the half-times of elimination from serum. There are no relevant differences, as summarized in Figure 4.

Discussion and conclusions

Since no pharmacokinetic interactions after single doses of nomifensine and clobazam could be detected,

it seemed feasible to extrapolate the results to multiple dose kinetics. The following assumptions were made (Table 1): oral doses of nomifensine 25 mg and clobazam 7.5 mg are given at intervals of 8 hours. Peak concentrations of nomifensine are measured 2 h, and of clobazam 4 h after medication. The half-time for elimination of nomifensine is 2 h, and of clobazam 18 hours.

What can be expected from the pharmacokinetic point of view is shown in Figure 5. Due to the short half-time, there is a relatively wide fluctuation between minimum and maximum concentrations of nomifensine, but there is no accumulation. On the other hand, clobazam accumulates until a steady state is reached after approximately 7 days.

What is the practical message mediated by these extrapolations? Do we have any evidence that this playing with figures is useful? Yes, we do. For instance, two matched groups of 18 depressed patients

Table 1 Extrapolated multiple dose kinetics for nomifensine and clobazam

Assumptions	Nomifensine	Clobazam
Dose (mg)	25	10 7.5
Peak level (µg/ml)	0.2	0.15 0.13
Time of peak (h)	2	4 4
Half-time for elimination (h)	2	18 18
Dose interval (h)	8	8 8

were treated by Radmayr (personal communication) either with nomifensine 25 mg or with the combination nomifensine 25 mg plus clobazam 10 mg three times daily. Whereas nomifensine alone did not

influence the ratings of the Hamilton Anxiety Scale, the mean scores of the group treated with the drugs in combination were significantly lower at day 7 of medication.

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