ASTRA
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NAME OF COMPANY ASTRA HÄSSLE AB TRADE NAME(S) NAMES OF ACTIVE INGREDIENT(S) INN H 199/18 and diazepam	**Clinical Study Synopsis** REFERENCE IN THE DOSSIER VOLUME REF. NUMBER PAGE	(FOR NATIONAL AUTHORITY USE ONLY) STUDY CODE SH-QBE-0003 REPORT NO. SH-QBE-0003

TITLE OF THE STUDY

PHARMACOKINETICS OF DIAZEPAM WITH AND WITHOUT CO-ADMINISTRATION OF H 199/18 SODIUM IN HEALTHY VOLUNTEERS

STUDY CENTRE

Quintiles AB, Islandsgatan 2, S- 753 18 Uppsala, Sweden
(former PMC Drug Study Unit AB)

STUDY PERIOD

April 20 - June 21, 1995

CLINICAL PHASE

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OBJECTIVES

The aim of the study was to investigate the pharmacokinetics of diazepam and the formation of one of its active metabolites, N-desmethyldiazepam, after a single i.v. dose, during repeated oral administration of H 199/18 or placebo in healthy subjects.

STUDY DESIGN

The study was conducted as a double-blind, randomised, two-way cross-over trial in which each subject received 30 mg H 199/18 given as its corresponding sodium salt in a solution or placebo solution once daily for 9 days. On day 5 a single dose of diazepam, 0.1 mg/kg, was administered as a short term i.v. infusion.

NUMBER OFSUBJECTS

Ten healthy male subjects

DIAGNOSIS AND CRITERIA FOR INCLUSION

Inclusion criteria: male, 20 - 40 years of age, normal laboratory and physical findings prior to the study entry and signed informed consent.

INVESTIGATIONAL PRODUCT

Each subject received 30 mg H 199/18 (batch No. H 1103-1-2-1) given as its corresponding sodium salt in a solution once daily for 9 days. On day 5 a single dose of diazepam, 0.1 mg/kg, (batch No. H 1150-1-1-2) was administered as a short term i.v. infusion.

REFERENCE THERAPY

placebo (batch No. H 1163-1-1-1)

DURATION OF TREATMENT

Nine days

ASSESSMENT METHODS

The subjects were given either 30 mg H 199/18 or placebo once daily for 9 days. On day 5 a single dose of diazepam, 0.1 mg/kg, was administered as a short term i.v. infusion. Plasma concentrations of H 199/128, diazepam and N-desmethyldiazepam were analysed.

STATISTICAL METHODS

A mixed analysis of variance model was used. The result was stated as 95% confidence intervals for the mean ratios and p-values for the corresponding tests.

SUMMARY OF RESULTS

H 199/18 significantly increased the area under the plasma drug concentration-time curve from time 0 to infinity (AUC) of diazepam from 19.8 to 35.9 µmol*h/L ($p< 0.01$). Plasma clearance (CL) decreased from 1.3 to 0.7 L/h ($p<0.01$). The change of diazepam exposure during H 199/18 indicates a drug interaction.

The AUC_{0-t} of N-desmethyldiazepam after H 199/18 (10.5 µmol*h/L) was lower than after placebo (12.7 µmol*h/L) with p-value= 0.03.

The AUC values of H 199/18 were 3.4 and 7.9 µmol*h/L, respectively, on days 1 and 5 ($p<0.0001$). The C_{max} value on day 5 was also higher than on day 1. This change in H 199/18 exposdure indicates a decrease in drug metabolism with time.

No serious adverse events were reported after repeated doses of H 199/18 together with a single dose of diazepam.

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