Pharmacokinetics and Side-Effects of Clonazepam and Its 7-Amino-Metabolite in Man

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Summary. Clonazepam (CNP) and its principal metabolite in plasma, 7-amino-CNP (ACNP), have been investigated in a prospective study of 27 newly diagnosed epileptics and correlated with specified side-effects. At a daily dose of 6 mg, the average plasma levels of both substances were about 50 ng/ml, and individual values ranged from 30 to about 80 ng/ml. There was a linear correlation between changes in dose and the resulting plasma levels, which indicates first order elimination kinetics. Side-effects were frequent, but neither their severity nor their occurrence could be related to plasma levels or to the rate of increase in plasma concentration of the drug. Three out of five patients who developed serious dysphoria had significantly high CNP levels. The concentration of ACNP was considerably increased in four patients who subsequently suffered from withdrawal symptoms. Drug interaction with diphenylhydantoin, i.e. decreased CNP level, was observed in all five patients who received both compounds. In general it is not yet possible to define an upper limit for the plasma levels of CNP and ACNP at which toxicity occurs. In patients treated with conventional doses of CNP, measurement of plasma concentration is not required, except in special circumstances, because of the lack of correlation between plasma level and side-effects.

Key words. Clonazepam, 7-amino-clonazepam, pharmacokinetics, side-effects, man.

Clonazepam (CNP), 5-(2-chlorophenyl)-1,3 dihydro-7-nitro-2H-benzodiazepin-2-one (Rivotril®), has an anti-epileptic effect after oral administration. Its pharmacokinetics in man have only been studied in few investigations (Eschenhof, 1973; Huang et al., 1973; Naestoft et al., 1973), of which the last two alone were concerned with the relation between plasma level and effects. The occurrence of side-effects has not previously been correlated with the kinetics of CNP.

The most prominent side-effects are drowsiness and disturbances of coordination, often seen shortly after the start of medication and usually at a time when the dose is being increased. Thus, Elian et al. (1973) suggested that the rate at which the dose of CNP was increased could be correlated with the occurrence of its side-effects.

In order to clarify the pharmacokinetics of this drug and to define the minimum plasma level at which signs of toxicity would appear during the usual dosage regimen, a prospective phase 2-type trial was undertaken. It was based on gas-chromatographic assay of CNP and its major metabolite, 7-amino-clonazepam (ACNP; Larsen and Naestoft, 1974).

Material and Methods

Patients and Design of the Study

27 patients (10 female and 17 male) with newly diagnosed epilepsy were studied; their ages ranged from 12-71 years, average 39 years. As the type of seizure was considered of little importance in this study, patients with any kind of epileptic fit were accepted. Patients in whom an intracranial tumour was suspected were excluded. A routine clinical and biochemical screen showed that none suffered from any other disease. None of the patients had been treated before with anticonvulsants, no other medicine had been given three
The method used was capable of measuring CNP and its metabolites in plasma after a therapeutic dose. However, only the 7-amino-metabolite was found in appreciable amounts in plasma.

The compounds were extracted with ethyl acetate from a 2 ml plasma sample. After evaporation of the organic phase, the residue was dissolved in hydrochloric acid and washed with hexane. After neutralization CNP was extracted with toluene and the metabolites with a mixture of toluene and ethyl acetate (1:1). The extracts were concentrated by evaporation and injected into a gas-chromatography equipped with an electron capture detector. The internal standards employed were Ro 5-4435 for hydrochloric acid and washed with hexane. After injection the metabolites were measured by a gas-chromatograph equipped with an electron capture detector.

In urine CNP, 7-amino-CNP, 7-acetamino-CNP and their 3-hydroxy-derivatives were measured by a slight modification of the plasma assay.

The technical details of the analytical procedure have recently been described by Naestoft and Larsen (1974).

Statistical Methods

The main problem, the correlation of side-effects with plasma concentration, was examined by a sequential rank-correlation test, constructed on the basis of simulation results, and by a sequential analogy to the Wilcoxon-Mann-Whitney test with the Lehmann alternative. The remaining problems were examined by testing a large number of combinations of variables by non-parametric fixed sample tests: Spearman rank-correlation test, Kruskal-Wallis rank-variance analysis, Wilcoxon-Mann-Whitney test, chi-square test and the Friedman rank variance analysis. An IBM 1800 computer was used.

Record of Side-Effects

The following side-effects were sought by examination and interviews, according to a special questionnaire: 1) Drowsiness; 2) Incoordination of gait, both according to the patient's own complaints and as observed by the physician and nurses; 3) Euphoria; 4) Dysphoria; 5) Irritability; 6) Changes in libido and sexual potency; 7) Impairment of memory; 8) Visual disorders; 9) Hypotonia; 10) Dizziness; and, 11) Abnormal thirst.

The side-effects were scored in the following manner: 1) Drowsiness and 2) Incoordination in gait on a scale of 0-3, both from the patient's own complaints and from observed side-effects.

Items 3) - 11) were scored as 0 or 1, according to their absence or presence.

The study was not carried out as a blind trial, so considerable bias and influence of placebo-effects on the results must be suspected. In order to avoid at least some of these effects, the patients were also evaluated for side-effects before medication and always by the same physician (O.S.). Furthermore, the results of the plasma analyses were not made available to him until after the trial had been concluded.