NEW DRUG APPLICATION

SUBMITTED TO THE ERICIAN REGISTRATION COMMITTEE (CLINICAL SECTION)

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REJUVENAL

500 mg. tablets

BACKGROUND INFORMATION

Rejuvenal is the proposed trade name for: Methyl-nicotinyl-aminoethyl para-chlorophenoxylysergamide.

This broad-spectrum geriatric agent was rejected by the Erician Committee in 1972, primarily because the clinical material was considered to be based only on case histories and testimonials, and because kinetic data were felt to be insufficient. The present submission is therefore based exclusively on the results of new studies which the company believes will meet the committee's standards.

The animal pharmacological and toxicological file has not been supplemented, since in 1972 no objections were raised by the committee in that field, three-month toxicity studies in two species having demonstrated no noxious effects.

HUMAN PHARMACOLOGY (SUMMARY)

1. Pharmacodynamics

The mechanism of action of this new molecule is not known, and no claims will be advanced in this direction. Animal studies point to effects both on the central nervous system (stimulation) and the cardiovascular system (vasodilation) but it is not clear to what extent these findings are relevant in the human situation.
2. Kinetics

Drambuie et al. have reported to us on a study in 16 healthy volunteers in the Ruritanian Military Prison. All subjects received a single oral dose of 500 mg Rejuvenal in encapsulated form, the latter being chosen because of technical problems in tableting labelled material. The nicotinyl moiety was labelled with tritium, the chlorophenoxy moiety with Cl4; the lysergamide moiety was studied in body fluids by gas chromatography using a method developed in our own laboratories. Plasma determinations were performed at intervals of 15 minutes up to one hour, then hourly up to 36 hours.

Rejuvenal is very promptly absorbed, maximal levels of each of the three moieties traced being found in the plasma at the 15th minute after ingestion. There would appear, however, to be a very considerable first-pass effect, probably involving the liver, since the levels of the moieties found are not proportional to those in the original molecule, and the discrepancy increases rapidly with time. The role of the liver is suggested particularly by the fact that the discrepancies were much greater in two subjects receiving high doses of barbiturates for reasons unconnected with the study. The results in 14 subjects are indicated below; material from one subject was mislaid, and a second subject died during the course of the study (mors subita e causa ignota). See table K.

At the 36th hour, 82% of the total radioactive dose had appeared in the urine (for Cl4 75-88%, for H3 72-92%), with only traces in the faeces.

A follow-up in two trial subjects continuing up to the seventh day suggested that elimination of the remaining radioactivity is progressive, the total percentage of radioactivity excreted increasing in one subject during the 2nd-7th days from 70% to 74% and in the other from 84% to 90%.

CLINICAL THERAPEUTIC STUDIES

1. Keflavik (Iceland) performed a double-blind placebo controlled randomised crossover trial over patients with intermittent claudication. The parameters used were approved by Prof. Peter Armitage (Oxford) and Prof. Franz Gross (Heidelberg). The study

| TABLE K |
| Plasma elimination T 1/2: |
| tritium labelled material | 45 minutes (± SD 22) |
| Cl4-labelled material | 670 minutes (± SD 330) |
| lysergamide moiety | 900 minutes (± SD 205) |