CHAPTER 19

Lisuride Pharmacology and Treatment of Parkinson's Disease

G. GOPINATHAN, R. HORIZON and I. H. SUCHY

A. Chemistry

Lisuride hydrogen maleate [1,1 diethyl-3-(9,10-didehydro-6-methyl-8α-ergoliny1] urea is the first derivative of isolysergic acid in clinical use. It is an 8-α-aminoergoline and was synthesized by ZIKAN and SEMONSKY (1968). It is a white slightly bitter tasting substance, which is reasonably stable at room temperature if not exposed to light. Lisuride hydrogen maleate is soluble in water or saline up to 1 mg/ml. Owing to its low effective dose, it is therefore the first dopamine agonist which can also be used on a parenteral basis (BARROW et al. 1980).

\[
\begin{align*}
\text{Et} & \quad \text{N} \quad \text{CO} \quad \text{HN} \\
\text{Et} & \quad 2 \quad 3 \\
\text{Et} & \quad 13 \quad 12 \quad 11 \quad 10 \quad 9 \quad 8 \quad 7 \quad \text{H} \\
\text{N} & \quad 5 \quad \text{CH}_3 \\
\end{align*}
\]

B. Toxicology

The acute LD50 in mice is 90 mg/kg p.o. and 14.4 mg/kg i.v. while in rats it is 10–15 mg p.o. and 1–2 mg/kg i.v. There is a large safety range if one considers that the effective oral doses in rats (e.g. reserpine antagonism and lowering of prolactin) are in the range of 0.01 mg/kg or below. In the monkey, doses up to 200 mg/kg p.o. did not kill the animals. Chronic toxicity studies in monkeys and rats did not reveal organ damage at 5 and 10 mg/kg p.o.

Carcinogenicity studies in rodents revealed a dose-dependent reduction of the incidence of pituitary and mammary tumours. More animals in the treatment groups survived the 2-year study than in the control group. There was no increased incidence of endometrial carcinomas. In a small percentage of male rats in the highest dose groups, Leydig cell hyperplasia or adenomas were observed. There was no indication for embryotoxic or teratogenic effects; only nidation and lactation in rats was impaired owing to the prolactin-lowering effect of lisuride (G. SCHUPPLER and P. GÜNZEL 1984 personal communication).
C. Pharmacokinetics

Lisuride is completely absorbed from the gut in laboratory animals as well as in young volunteers (Huempel et al. 1981) and old volunteers (Huempel 1983). It is in part metabolized during its first pass through the liver. The clearance rate has been found to be $0.80 \pm 0.25 \text{l/min}$ in volunteers. In patients with Parkinson's Disease, individual clearance values derived from the estimated AUC (area under the curve) ranged from $0.39-7.13 \text{l/min}$ ($\bar{x} = 1.95 \pm 1.99$). There is a moderate enterohepatic circulation (Burns and Calne 1981; Burns et al. 1984). Metabolism occurs in various ways via oxidative desalkylation, hydroxylation, mono-osygenation, and oxidation. No metabolite accounted for more than 10% of the high pressure liquid chromatography spectrum. It is unlikely that metabolites contribute to the pharmacological effects of lisuride. They are excreted via urine and faeces in varying proportions, mainly via urine as is the case with most ergolines (Burns and Calne 1981).

The proportion of lisuride that becomes systemically available varies from one individual to another more than within individuals. On the average, bioavailability has been found to be 10%-20%. The first-pass effect and the resulting bioavailability depend on individual liver plasma flow and the state of the microsomal enzyme activity in the liver. From one clinical trial a 100% increase of clearance rate during a 2 to 4 week treatment has been reported (Burns et al. 1984). There is no indication for enzyme induction in chronic treatment (Carruba et al. 1985). Inhibition of liver microsomal enzyme activity by proadifen has been shown to prolong and intensify the motor action of lisuride in laboratory animals (Keller and Da Prada 1979).

Peak plasma levels after oral ingestion were reached at $39 \pm 28 \text{ min}$ in fasted PD patients (Burns et al. 1984). Similar times were observed in other trials when lisuride plasma levels were determined by a specific radioimmunoassay. After the use of $[^{14}\text{C}]$lisuride in old volunteers it was as long as 2 h (Huempel 1983). Volume of distribution has been calculated to be 2.3-2.4 l/kg which would mean that lisuride passes readily into the tissues. The time for distribution into the tissues, according to the $\beta$-phase of elimination from the plasma after i.v. injection, is 20-30 min.

Lisuride passes quickly through the blood-brain barrier into the brain where it binds to various neuronal receptors. In animal experiments the maximum level of radioactivity in the brain of the rat has been seen 15 min after i.v. injection. Brain levels of lisuride (in animals) decrease more slowly than plasma levels. From 30 min to 8 h after injection there was more radioactive material in the brain than in the plasma. Autoradiographic studies in rats with tritiated lisuride show highest levels of radioactivity 60 min after injection in caudate, putamen, parts of the thalamus and layer IV of the cortex (ratio 3-4.5:1 in corpus callosum; Stumppf et al. 1985). From experiments in rabbits it is known that $[^{14}\text{C}]$lisuride levels in the pituitary are ten times higher than those in putamen or other brain areas (Dorow et al. 1983). Onset of action after intravenous injection was 10 min for the motor system of PD patients (Parkes et al. 1981) and 30 min for the prolactin-lowering effect (Dorow et al. 1981).