TOXICOLOGY OF CLOBAZAM

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- 1 Extensive toxicological investigations of clobazam are summarized.
- 2 LD₅₀ values after oral administration ranged from 100 mg/kg in the dog to 6000 mg/kg in the rat.
- 3 Long-term repeated dose studies have shown withdrawal effects in the dog and monkey (notably convulsions leading to death), similar to those known to occur with other benzodiazepines.
- 4 It is concluded that the overall safety and tolerability of clobazam have been demonstrated in the preclinical animal studies.

Acute toxicity

THE acute toxicity of clobazam (Table 1) has been determined orally in rats, mice, rabbits, guinea pigs and dogs, and parenterally (subcutaneously and intraperitoneally) in rats and mice. Administration of sufficiently large intravenous doses was not possible because of the poor solubility of the drug. Dogs could not be given fatal doses of clobazam orally because large doses were vomited. Some studies were carried out several times in different laboratories and with animals of varying ages and strains. The toxicity picture was uniform. Sedation, trembling, lachrymation, ataxia, reflex reduction and narcosis were observed, which eventually resulted in the death of the treated animals. The time course depended on the route of administration.

Repeated dose toxicity

Repeated dose toxicity studies of varying duration

were carried out orally in dogs, rats and monkeys.

Rats (Table 2)

Rats were dosed daily with clobazam for 1, 6 or 18 months. The drug was administered either suspended in starch mucilage by oral gavage or mixed in the food in doses equivalent to 12–1000 mg/kg bodyweight. Pharmacological activity was exhibited in a dose-dependent reduction of spontaneous activity and sedation which, after higher doses of clobazam, also resulted in the eventual reduction of food intake and reduction of weight gain.

Most rats which died intercurrently in the 18-month feeding studies showed lung changes which were unrelated to the drug.

After oral gavage, 4 out of 18 male rats in the 100 mg/kg group and 3 out of 18 male rats in the 400 mg/kg group in a 6-month study showed lateral positioning between test days 60 and 153. Death

Table 1 Acute toxicity of clobazam

Animal	Dose route	LD ₅₀ (mg/kg)
Rat	Oral	6000 (4880–7380)
	Intraperitoneal	1. 740 (661– 829)
	Intraperitoneal	2. 1526 (1308–1781)
	Subcutaneous	> 5000
Mouse	Oral	1. 640 (547– 749)
	Oral	2. 1101 (1044–1161)
	Oral	3. 680 (504– 918) ♂
		820 (686– 980) ♀
	Intraperitoneal	1. 289 (259– 321)
	Intraperitoneal	2. 510 (442– 586) ♂
		615 (535– 708) ♀
	Subcutaneous	2250 (1666–3020) ♂
Rabbit	Oral	2500 ♀
		320 (269– 381)
Guinea-pig	Oral	109 (76– 157)
Dog	Oral	> 100 (vomiting!)

Table 2 Long-term studies in rats

<i>Dose (mg/kg)</i>	<i>Route</i>	<i>Duration</i>	<i>Male deaths</i>	<i>Female deaths</i>	<i>Remarks</i>
0	Gavage	1 month	0/10	0/10	
100			0/10	0/10	
400			1/10	0/10	
1000			1/10	0/10	
0	Gavage	6 months	1/18	0/18	
25			0/17	0/17	
100			4/18	0/18	
400			3/18	0/18	
0	In food	6 months	0/10	0/10	
12			0/10	0/10	
35			0/10	0/10	
100			0/10	0/10	
0	In food	18 months	5/30	4/30	After 2 weeks 200 mg/kg
17			3/30	4/30	After 22 weeks 400 mg/kg
35			3/30	2/30	After 2 weeks 200 mg/kg
100			5/30	4/30	After 36 weeks 600 mg/kg

occurred following respiratory depression and fall in body temperature. In surviving rats, apart from piloerection, there were no significant clinical, clinico-chemical or haematological findings. After the higher dose treatment, liver weight was increased due to the proliferation of the smooth endoplasmic reticulum. The latter phenomenon was more pronounced in males than in females. Associated with it, there was an increase in the activity of drug-metabolizing enzymes. The thyroid glands also showed an increase in weight. Histological examination showed signs of hypofunction of the gland. Both changes showed signs of being reversible after withdrawal of the drug. The elevation of the adrenal and ovarian weights in some animals and the reduction in seminal vesicle weight in others occurred without histological changes.

Dogs (Table 3)

Dogs received clobazam over 6, 12 or 16 months daily in oral doses of 2.5–80 mg/kg bodyweight, ad-

ministered in capsules. The animals showed dose-dependent sedation, somnolence, ataxia and light tremor. These symptoms subsided almost completely after a short time. Elevation of serum alkaline phosphatase was seen in the highest dosage group. This finding, however, was not associated with any liver damage. A slightly increased accumulation of pigment was noted in the hepatocytes and Kupffer cells. Repeated convulsions and several dose-dependent deaths were observed. Continual observations, withdrawal studies and electroencephalography of dogs in which rhinencephalon electrodes had been implanted, showed that the convulsions and death should be regarded as a result of withdrawal symptoms. In this connection the main metabolite of clobazam, the *N*-desmethyl compound, was tested and the same withdrawal symptoms observed. Similar observations have been made with other benzodiazepines. Further pathological, clinical, clinico-chemical or haematological abnormalities were not detected.

Table 3 Long-term studies in dogs

<i>Dose (mg/kg)</i>	<i>Route</i>	<i>Duration</i>	<i>Male deaths</i>	<i>Female deaths</i>	<i>Remarks</i>
0	Capsule	6 months	0/3	0/3	
5			0/3	0/3	
20			1/3	0/3	
80			1/3	1/3	One female died independently of drug effect (parasites)
0	Capsule	12 months	0/4	0/4	
5			2/4	0/4	
10			2/4	0/4	
40			3/4	2/4	One male accidentally killed in week 29
2.5	Capsule	12 months	0/4	0/4	
5			0/4	0/4	

Monkeys (Table 4)

Rhesus monkeys received a daily oral dose of 2.5–20 mg/kg bodyweight by oral gavage over 10 weeks or 12 months. They developed dose-dependent sedation without tolerance, reduced heart rate, ataxia, and coordination disorders. The withdrawal symptoms observed after clobazam were not so marked as those induced by diazepam. One male animal in the 20 mg/kg group died, as did one in the 7.1 mg/kg group without necessarily being drug-dependent. Drug-related clinical, clinicochemical, haematological or histological findings were not observed.

Special studies. Studies with a special self-injection technique, also in Rhesus monkeys, showed no evidence of addictive potential with clobazam.

Reproductive toxicity (Table 5)

In reproductive toxicity studies in rats and mice clobazam was without teratogenic or fertility-

disturbing effect. Rats reared their litters normally but mice showed a dose-dependent decrease in rearing rate with the mothers neither severing the umbilical cord nor suckling their young. It may be concluded that this behaviour was due to the sedative action of the drug.

Conclusions

Extensive toxicology studies, together with the pharmacological, kinetic and metabolic studies which have been carried out, have shown a good overall tolerance for clobazam.

The studies reported here were carried out in the research departments of Hoechst-Roussel Pharmaceuticals Inc., Somerville, New Jersey, USA; Hoechst Japan Ltd, Tokyo, Japan; the Laboratorium für Pharmakologie und Toxikologie, Hamburg, BRD (Professor Leuschner); Institute of Comparative and Human Toxicology, Albany, New York, USA and Hoechst AG, Frankfurt am Main, Federal Republic of Germany.

Table 4 Long-term studies in monkeys

<i>Dose (mg/kg)</i>	<i>Route</i>	<i>Duration</i>	<i>Male deaths</i>	<i>Female deaths</i>
0	Gavage	10 weeks	0/2	0/2
5			0/2	0/2
10			0/2	0/2
20			0/2	0/2
0	Gavage	12 months	0/4	0/4
2,5			0/4	0/4
7,1			1/4	0/4
20,0			1/4	0/4

Table 5 Reproductive studies

<i>Test</i>	<i>Species</i>	<i>Dose</i>	<i>Route</i>
Segment I Fertility	Rat	0, 40, 200, 1000 p.p.m.	In food
	Mouse	0, 40, 200, 1000 p.p.m.	In food
Segment II Teratogenicity	Rat	0, 25, 100, 400 mg/kg	Gavage
	Mouse	0, 6, 25, 100 mg/kg	Gavage
Segment III Peri-postnatal development	Rat	0, 5, 32, 200 mg/kg	Gavage