

## BENZODIAZEPINE WITHDRAWAL

Key-words: Pharmacodependence, Drug abuse, Benzodiazepine, Withdrawal, Diazepam

### Rationale

Due to their dependence potential, benzodiazepines often lead to abuse consumption. Like for others new drugs dedicated to the treatment of CNS pathologies, the evaluation of the potential dependence of benzodiazepines is necessary. To illustrate their addictive properties, chronic treatment with benzodiazepines leads to a physical dependence state which can be characterized by physical signs following withdrawal. The observation of the physical signs induced by withdrawal is considered as a relevant evaluation of the dependence potential of benzodiazepines.

**Following a chronic treatment with a benzodiazepine in mice,** the withdrawal is precipitated by administration of a benzodiazepine antagonist, flumazenil. The physical signs induced by withdrawal are measured.

**Method** – Swiss male mice are treated intraperitoneally with either vehicle or diazepam twice daily (at 9h and at 17h) for nine consecutive days. Initially, on day 1, diazepam-treated subjects receive a dose of 50 mg/kg/injection and the dose of diazepam is increased by 50 mg/kg, for nine consecutive days (450 mg/kg/injection on day 9). On day 10, sixteen hours after the last injection, precipitated withdrawal is induced by administration of flumazenil (10 mg/kg; IP) and the mice are observed for the next 30 min. Withdrawal symptoms are recorded and a global withdrawal score is calculated for each individual animal according to the method of Toki et al. <sup>(1)</sup>, as indicated in Table 1.

**Table 1 – Withdrawal scores**

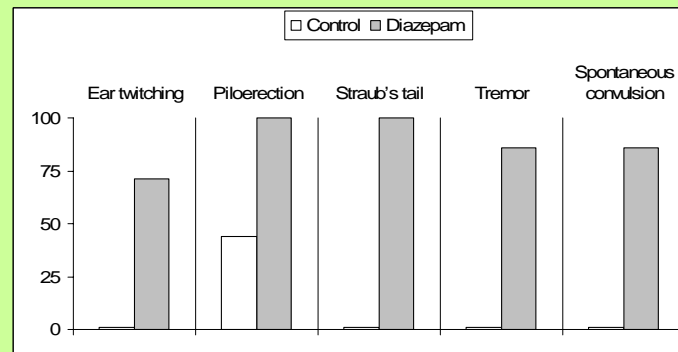
Items	Score
Weight loss 5-10%	1
Weight loss > 10%	2
Vocalization	2
Irritability	2
Muscle rigidity	2
Ear twitching	2
Piloerection	2
Straub's tail	2
Fascicular twitch	3
Nosbleed	3
Agression	3
Tremor	3
Spontaneous convulsion	4
Death	4

### Reference;

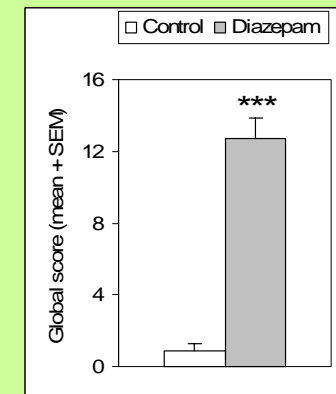
1. Toki S et al., Life Sci. 59:1631-1641, 1996.

**Results** – Flumazenil-precipitated diazepam withdrawal induces numerous signs (Fig. 1) and dramatically enhance the global withdrawal score (Fig. 2).

**Figure 1 – Percentage of animals exhibiting various signs after flumazenil injection**



**Figure 2 – Global benzodiazepine withdrawal score after flumazenil injection**



Difference vs. control group \*\*\*  $p < 0.001$