Toxicodynetics of mono-intoxications with oxazepam and nordiazepam. An approach to a better understanding of drug-drug interaction

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Introduction

• Among the drugs reported to be involved in self-poisonings, benzodiazepines remain the leading class of psychotropic drugs (1, 2).

• However, the pharmacology and the toxicology as well of these drugs remain complex due to a chain of active metabolites with a final pathway frequently involving nordiazepam and oxazepam.

• In spite of the progressive withdrawal of potent hypnotics, drug-induced coma remains a leading and even increasing cause of admission in intensive care units (3).

As oxazepam and nordiazepam are frequently involved in drug overdose, either as the toxicants by itself or active metabolites, we feel mandatory to assess their respective toxicodynetics.

What is toxicodynetics? A new discipline of clinical toxicology aiming at a systematic description of the time-course of major clinically relevant toxic effect in overdose

What are major clinically relevant toxic effect in overdose with nordiazepam or oxazepam?

Disturbances of the central nervous system
Toxicodynamics of mono-intoxications with oxazepam and nordiazepam. An approach to a better understanding of drug-drug interaction

**Materials and methods**

Data collected at the Paris Poison control centre (PPCC) from 1999 to 2015.

The classical toxicodynamics parameters were looked for using the individual medical record available at the PPCC.

- 1) the supposed ingested dose which was expressed as a therapeutic index (TI) as defined by a percentage of the maximum recommended daily dose,
- 2) the time of ingestion (T0), the delay in onset (hours),
- 3) the rate of worsening (hours or on-off process),
- 4) the maximal observed effect (Emax),
- 5) the time of onset of the maximal effect (Tmax),
- 6) the shape of the duration of maximal effect as a peak or a plateau,
- 7) the rate of recovery,
- 8) the duration of hospitalisation in uncomplicated poisonings.
Results (1/3)

Data collected at the Paris Poison control centre (PPCC) from 1999 to 2015.

The number of included mono-intoxication with oxazepam and nordiazepam poisonings were 257 and 74 cases, respectively.

The T0 was known in all cases (100%).

The Emax in both oxazepam and nordiazepam was sleepiness or obtundation occurring in 108 and 36 cases of nordiazepam and oxazepam, respectively.

Noteworthy, coma was never used to qualify alteration in consciousness of the poisoned patients.

Results (2/3)

The number of included mono-intoxication with oxazepam and nordiazepam poisonings were 257 and 74 cases, respectively.

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Results (3/3)

• The median delay in onset was 1 h in both poisonings.
• Interestingly in both poisonings there was no reported delay in onset of the Emax which was reported on a “on-off” mode.
• The median TI resulting in the Emax effect was 19.6- and 3.3-fold the maximum recommended daily dose in nordiazepam and oxazepam poisonings, respectively.
• Data from the PPCC were unable to describe the late phases of dynetics (phases 6 to 8). Indeed, long-term follow-up of the poisoned patients was performed in only 13 and 19 % of the nordiazepam and oxazepam poisonings, respectively.

Discussion conclusion.

• The class of may cause altered consciousness in overdose.
• However, what is actually known for each substance? The toxicity greatly varied depending on the benzodiazepines:
  Oxazepam was shown to be safe meanwhile Temazepam was shown to cause coma (Buckley, Dawson et al. 1995)
  Alprazolam is the most frequent benzodiazepine reported in acute poisonings admitted in ICU (Isbister, O'Regan et al. 2004)

The results of the present study confirm the safety of oxazepam and extent to nordiazepam. Coma in presence of this benzodiazepine requires to look for associated toxicants.

Toxicodynamic approach appears useful to assess the time-course of relevant clinical effects
PCCs should improve long-term follow-up to be able to conclude about the global safety of a drug.