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Meprobamate Poisoning: Assessment of Risk Reduction Measures through French PCC Data

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BACKGROUND (1)

Meprobamate (*MEPRO* in this study)
- Equanil®, Quanil®, Mepro®, Meprodil®, Miltown®, Neuramate®, Mildaun®, Microbamat®…
- Major and active metabolite of carisoprodol

Carisoprodol
- Soma®, Somadrii®, Carisoma®, Myolax®, Somacid®… combined with aspirine: Sodol®, Soridol®, Soprodol®…
- “a centrally acting skeletal muscle relaxant whose mechanism of action is not completely understood but may be related to its sedative actions” (Martindale, 36th ed.)
**BACKGROUND (2)**

- MEPRO “is a carbamate with hypnotic, sedative and some muscle relaxant properties... It has been used in the short-term treatment of anxiety disorders, and also for the short term management of insomnia” (Martindale, 36th ed.)

- Acute MEPRO poisoning may be life-threatening:
  - deep and prolonged coma
  - severe vasoplegic or cardiogenic shock

- MEPRO has been (was...) marketed in France as:
  - an anxiolytic drug (MEPRO-ANX) mainly used in alcohol dependence
  - a hypnotic drug (MEPRO-HYP) (with aceprometazine)
BACKGROUND (3)

- In order to reduce the frequency and severity of MEPRO self-poisoning cases, French Health Products Safety Agency (Afssaps) took risk reduction measures (RRM) and limited:
  - in 2006, therapeutic uses
  - in 2009, the packaging size

  for MEPRO-ANX

  but not for MEPRO-HYP

- Afssaps asked the French National Coordination Committee for Toxicovigilance to assess RRM effectiveness
OBJECTIVES

Studying the annual course of MEPRO-ANX and MEPRO-HYP poisoning cases recorded by the French poison and toxicovigilance centres (PCC)

MATERIAL & METHOD

- Retrospective study
- All MEPRO exposure cases from 2000 to 2010
- Severe cases: convulsions, coma, collapse, arrhythmias, cardiac arrest, acute pulmonary oedema, bradypnoea/apnoea, respiratory distress or death
- PCC overall activity and MEPRO sales data were used as statistical adjustments
## RESULTS (1)

From 2000 to 2010: 12,870 cases

- 5,975 related to **MEPRO-ANX**
- 6,341 related to **MEPRO-HYP**
- 308 related to both drugs
- 246 of unspecified drug

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<tr>
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<th>Symptomatic</th>
<th>Severe</th>
<th>Death</th>
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<tbody>
<tr>
<td>MEPRO-ANX</td>
<td>67.0%</td>
<td>18.8%</td>
<td>0.9%</td>
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<tr>
<td>MEPRO-HYP</td>
<td>69.2%</td>
<td>23.2%</td>
<td>1.4%</td>
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<td>80% related to a suicide attempt</td>
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Symptomatic Severe Death

67.0% 18.8% 0.9%
69.2% 23.2% 1.4%
RESULTS (2)

Adjustment factors

- PCC activity (only drugs)
  
  Fig. Annual course of any drug exposure cases collected by PCC

- Sales data
  
  Fig. Annual course of MEPRO-ANX and MEPRO-HYP sales
RESULTS (3)

Fig. Annual course of MEPRO-ANX and MEPRO-HYP exposure cases adjusted on PCC activity and drug sales

Fig. Annual course of severe MEPRO-ANX and MEPRO-HYP exposure cases adjusted on PCC activity (severe cases) and drug sales
RESULTS (4)

Fig. Rate of severe cases (MEPRO-ANX and MEPRO-HYP)

The increase in the number of severe MEPRO-HYP cases is not explained by the parallel increase of all the severe cases percentages (in both therapeutic indications).

Fig. Annual course of severe (MEPRO-ANX and MEPRO-HYP) cases related to a suicide attempt adjusted on PCC activity and drug sales

The increase in severe suicide attempts may explain the increase in the number of severe cases.
DISCUSSION

- Methodological limitations: causality
  (lack of analytical toxicology data; possible association with other agents)

- Anxiolytic use of meprobamate (MEPRO-ANX)
  - Regulatory decisions led to a significant decrease in sales and in the number and severity of meprobamate-Anx poisoning cases reported to the French PCC
  - In 2010, it was too early to assess the effects of packaging size reduction (implemented in 2009)

- Hypnotic use of meprobamate (MEPRO-HYP)
  - No regulation measures during the study
  - No reduction of sales
    - No changes in the annual number of cases
  - In contrast, an increased number of severe self-poisoning cases even after adjustments
**CONCLUSIONS**

- PCC data may be used to assess risk reduction measures.

- This study *a posteriori* justified the interest in risk reduction measures.

- Afssaps recently (March 2011) decided to withdraw meprobamate-containing drugs indicated as anxiolytic/hypnotic.