Are Low Doses of Antipsychotics Effective in the Management of Psychomotor Agitation? A Randomized, Rated-Blind Trial of 4 Intramuscular Interventions

BACKGROUND

- High-potency, second-generation antipsychotics, sometimes combined with benzodiazepines, are effective in controlling psychomotor agitation; however, unwanted adverse effects, which are sometimes severe and even life-threatening have been concomitantly described with their use.
- In an emergency setting an induction of sedation with high potency antipsychotics may impair detailed evaluation and monitoring of the medical condition underlying psychomotor agitation.
- The current goal of pharmacological intervention is the induction of tranquilization (defined as a significant reduction in symptoms of agitation and aggression) without the induction of deep or prolonged sedation, while keeping the patient calm yet completely or partially responsive with the lowest possible frequency of adverse effects.

OBJECTIVE

- To compare the efficacy and safety of four low-dose pharmacological interventions (haloperidol + promethazine; haloperidol + midazolam; ziprasidone; olanzapine) used to control psychomotor agitation, guided by clinical response.

METHODS

- **Design:** Single site, double-blind, controlled experimental, randomized parallel trial; Duration: 2 years
- **Inclusion criteria:** Patients of both sexes, between 18 to 60 years of age, who presented with an acute agitation state requiring medical attention for rapid tranquilization. All psychiatric conditions that could be associated with psychomotor agitation were included, with the exclusion of delirium.
- **Exclusion criteria:** Individuals with serious medical conditions, a diagnosis of delirium, or those with a documented contraindication that could be related to a life-threatening situation with the utilization of any of the drugs in the study.
- **Primary outcome measure:** The reduction of levels of psychomotor agitation as measured by changes in ACES and PANSS-EC scores and in vital signs, specifically pulse and blood pressure.
- **Secondary outcome measure:** The occurrence of adverse effects in the following 24 hours after initial medication administration as measured by the UKU Scale.
- 108 patients received one of the study treatments; rating of the level of tranquilization was not performed in 8 patients, and they were excluded from the final analysis
- **Drug regimens:** 100 patients randomly received one of the following intramuscular treatments upon presentation to the emergency department with psychomotor agitation. Up to two additional doses of the treatment could be administered at 30 and 60 minutes after initial dose if clinically necessary.
    - 27 patients received haloperidol (HLP) 2.5mg + promethazine (PMZ) 25mg
    - 25 patients received haloperidol (HLP) 2.5mg + midazolam (MID) 7.5mg
    - 25 patients received olanzapine (OLZ) 10mg
    - 23 patients received ziprasidone (ZIP) 10mg
- Immediately before administration of the treatment, patients were administered the ACES and PANSS-EC. These rating instruments were readministered 30, 60, and 90 minutes after the initial injection, regardless of the need for additional medication. Measurements of vital signs (pulse and blood pressure) were taken 30, 60, and 90 minutes after the initial intervention. The UKU Scale was administered within 24 hours after intervention.
- Power 80% with an alpha level of 0.05 to detect a different of at least 2 points on the ACES (assuming a SD of 2.30). This was calculated to be sufficient for at least 20 patients in each group.
- Data handling method was per protocol

RESULTS

- **Primary outcome measure:**
    - All treatments reduced agitation as measured by the ACES ($P<0.001$), with a non-statistically significant difference between the treatment groups ($P=0.079$), independent of the time since the intervention ($P=0.603$).

Contrast analysis pointed to a treatment effect of levels of tranquilization with the combination HLP+PMZ (P=0.035) and ZIP (P=0.043) that was lower than the treatment effects obtained by the combination HLP+MID, which did not differ from OLZ (P=0.604).
    - Statistically significant effects of tranquilization were observed over time with the measurements obtained by the PANSS-EC (P<0.001), without significant differences between treatment groups (P=0.216).
    - Statistically significant reduction in heart rate during the first 90 minutes (P=0.022) independent of treatment. Non-significant reduction in systolic blood pressure over time (P=0.170). Significant reduction in diastolic blood pressure during this period (P=0.008), regardless of treatment group (P=0.153).
- **Secondary outcome measure:**
    - Occurrence of at least 1 extrapyramidal symptom within 24 hours after drug intervention was observed in 20 patients treated with HLP+PMZ, 14 patients treated with OLP, 12 patients treated with ZIP, and 11 patients treated with HLP+MID.
    - Logical regression analysis showed that patients treated with HLP+PMZ had a significantly increased risk of developing extrapyramidal symptoms than those treated with HLP+HLP. Statistical significance remained even after other variables (prior psychotropic medication use, need for an additional dose, and ultimate psychiatric diagnosis) were included in the model.

STRENGTHS

- Parallel study design
- Both patients and investigators were blinded to the treatment throughout the study; unblinding was not likely
- Evaluators received standardized and systemic training on using the rating scales used in the study before the process of data collection commenced
- Due to the nature of the study, dropout was not an issue

LIMITATIONS

- There was variation in the clinical features between some the treatment groups at baseline
- Study was conducted at only one center
- Low-dosing of the study medications should have been more standardized, specifically in regards to the dose of midazolam
- 67% of patients had been medicated before admission to the emergency department

CONCLUSIONS

- Low doses of antipsychotics can be effective for the management of agitated patients without excessive sedation.
- Low-cost medications, such as haloperidol + short half-life benzodiazepine, might be as effective as new generation antipsychotics, without significant differences in extrapyramidal effects.
- In practice, the combination of haloperidol + promethazine should only be considered a second line option because of the risk of extrapyramidal effects.
- Future Research:
    - Additional multicenter studies with larger samples are needed to confirm the findings of this investigation.

REFERENCE: Mantovani C, Labate CM, Sponholz A, de Azevedo Marques JM, Guapo VG, de Simone Brito dos Santos ME, et al. Are Low Doses of Antipsychotics Effective in the Management of Psychomotor Agitation? A Randomized, Rated-Blind Trial of 4 Intramuscular Interventions. *J Clin Psychopharmacol* 2013;33: 306-312.

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