Study proposal for a Bayesian adjusted study to investigate the dose of antipsychotics resulting in a target exposure associated with anti-delirant effects with minimized occurrence of side effects.

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Background:
Delirium is an acute mental disturbance in critically ill patients associated with significant morbidity and mortality. Its prevalence is up to 40% in an ICU setting. If left untreated it can cause significant complications (i.e. auto-extubation), and has a poor prognosis as reflected by a prolonged lenght of stay (LOS), worse functional and cognitive outcome and a 20% higher mortality rate. Besides being a well known condition in adult and geriatric patients, it is increasingly recognized in children as well.
Treatment of delirium is often done with antipsychotics of which Haloperidol, risperidone and quetiapine are frequently used. However, little is known about the doses required to adequately treat delirium, inherently risking the possibility for underdosing (with lack of efficacy as a result) or overdosing and severe adverse events. Finding the right dose is complicated by concomitant diseases and/or medication and the need to extrapolate to different poplulations (i.e. pediatrics – geriatrics). The latter being necessary because different populations are likely to have differences in pharmacokinetics and differences in pharmacodynamic response. This project foresees a Bayesian adaptive design based on interim evaluations to efficiently identify the correct doses of antipsychotics to be used in delirium in pediatric and adult patients.

Target definition:
In adults, a clear relation between plasma-concentration and D2 receptor occupancy exists. This relation has been the basis for the use of anti-psychotics or decades whereas > 70% D2 receptor occupancy is associated with a decrease in clinical symptoms in schizophrenia. Although the relation between antipsychotic plasma-concentrations and their effects in delirium is less well established, the use of antipsychotics in delirium, in similar dosages as used for schizophrenia in the clinical setting implies a similar relation. As such, a plasma-concentration associated with 65-75% receptor occupancy can be pre-defined, which should also be the target for the (pediatric) use of antipsychotics in delirium. After each interim evaluation, dosing can be adjusted to target the above pre-defined plasma exposure of antipsychotics in (pediatric) patients.

Adaptive approach:
Following a Bayesian adaptation approach, exposure (plasma-concentrations) will be measured after each 3 patients with one antipsychotic drug. (Besides pharmacokinetic parameters, prolactin concentrations, ECG recordings, adverse events recording, as well as scales for the extrapyramidal side effects and the delirium outcome will be considered in the evaluation).
Potential confounding factors will be accounted for (if necessary, excluded from the interim evaluation, but included in the final evaluation)

In case the measured median exposure is higher or lower than the targeted exposure ±2SE, dosing in the next patients may be adjusted to reach the predefined target.

Objectives:
Primary:

- To determine a (weight adjusted) dose of antipsychotics that achieves a target plasma concentration corresponding to adequate D2 receptor occupancy and anti-delirant effects in adults with acceptable safety profile.

Study design:
This study will have an open label, (Bayesian adjusted) adaptive dosing design, whereby dosing will be adjusted to target an efficacious pre-defined plasma exposure of antipsychotics in pediatric and adult patients.
Prior to the study a (weight-adjusted) dose of antipsychotics will be defined, targeting an exposure range as described above.
The study population will consist of 22 pediatric patients (ages 0 – 18 years) and 22 adults patients on the (P)ICU with suspected delirium requiring antipsychotic treatment. No limitations are foreseen in concomitant diseases or concomitant medication, instead putative effects will be considered in the (interim) evaluations.
Interim evaluations will be performed after each 3 patients in the adult or pediatric group.
Prior to dosing the antipsychotic, baseline assessments of the delirium severity and extrapyramidal symptoms (frequently occurring adverse event) will be performed, and plasma prolactin will be measured. Furthermore, a baseline ECG will be recorded. The patient's condition and medication used will be adequately recorded at baseline.
After the first dosing of antipsychotics, blood samples for determination of pharmacokinetic parameters (Cmax, AUC and Cavg, Clearence) and prolactin concentrations will be drawn at predefined timepoints.
Assessments for Delirium severity, EPS, and ECG recordings will be performed at predefined timepoints. General adverse events will be evaluated continuously.

Question to the audience:
Any feedback is welcome, but specifically feedback on the total number of patients and the number for the interim evaluation would be appreciated.