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LETTER

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Adverse events of haloperidol for the treatment of delirium in critically ill children

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Dear Editor,

Delirium in critically ill children is increasingly recognized, with a reported prevalence of up to 29 % [1, 2]. The true prevalence of pediatric delirium (PD) may even be higher due to diagnostic challenges and previous lack of awareness amongst care-givers [1, 3, 4]. Its clinical significance is reflected by a relationship with negative patient outcomes [2, 3]. Haloperidol is currently the drug of choice for treating PD, despite a lack of data from both adult and pediatric studies supporting its efficacy [2, 3]. Its use is associated with the development of a wide range of adverse events (AE), ranging from mild to serious. Only limited data on the incidence and nature of AE in this population are available and most are derived from small study cohorts [3, 4].

The objective of this study was to investigate the frequency and nature of haloperidol-related AE in critically ill children with PD and to explore a possible dose–AE relationship.

We included children admitted to the ICU of Sophia Children's Hospital between January 2000 and July 2011 who received haloperidol for PD. Medical charts and our electronic patient data management system were evaluated for AE, based on a predefined list of known haloperidol AE including extrapyramidal symptoms, hyperpyrexia (including neurologic malignant syndrome), decreased level of consciousness, circulatory changes and ECG changes, in particular prolonged QTc interval. The probability of an association between symptoms and the administration of haloperidol was assessed using the Naranjo score [5] and evaluated by two clinical pharmacologists and the Dutch Pharmacovigilance Institute. Fifty-two children received haloperidol for PD. In five (9.6 %) of these children possible AE were identified. The probability of causality ranged from possible to definite. The majority of AE disappeared after reducing or discontinuing the drug, although information on long-term sequelae was lacking (Table 1). Interestingly, only female patients experienced AE, versus 22 of 47 (47 %) female patients in the non-AE group. There was no significant difference between patients with and without AE in age [median 6.3 years (range 3.9–15) vs 11.7 (0.25–18.8)], haloperidol dose [median 0.03 mg/kg/day (range 0.02–0.05) vs 0.02 (0.003–0.08)], or severity of illness as reflected by PRISM score [median 18 (range 0–23) vs 16 (2–40)].

In conclusion, a considerable proportion of critically ill children with PD appear to develop AE with haloperidol. The nature of the AE found in this study largely corresponds to the AE described by others. Furthermore, in adults a clear relationship exists between haloperidol plasma concentrations and D2-receptor occupancy. This steep concentration–response curve leads from a therapeutic response to toxicity. In critically ill children pharmacokinetic data are lacking, which hampers extrapolation from these adult data to develop evidence-based dosing guidelines. Prospective

Table 1 Characteristics of patients with AE

Patient	1	2	3	4	5
Age (years)	7	3	15	6	4
Gender	F	F	F	F	F
Primary diagnosis	Septic shock, meningitis	Respiratory insufficiency	Trauma (without head injury)	Respiratory insufficiency	Circulatory and respiratory insufficiency
AE	Decreased level of consciousness Tremor of all extremities Dystonia, lateralization	Oculogyric crisis Drooling Fever	Fever Tachycardia Suspected NMS	Oculogyric crisis Cogwheel rigidity	Muscle rigidity
Day of onset of AE after first dose of haloperidol	Day 3	Day 2	Day 1	Day 3	Day 2
Measures taken to mitigate AE	Dose lowered, later discontinued Symptoms improved after discontinuation	Biperiden day 2, same dose haloperidol continued Second dose biperiden day 4, after which symptoms resolved Haloperidol dose lowered after 2nd dose biperiden	Haloperidol discontinued Symptoms did not reoccur, nor after restarting haloperidol after 24 h	Biperiden, effect unclear Pentobarbital after which symptoms resolved Haloperidol discontinued	Dose lowered Symptoms resolved
Dose (mg/kg/day) before AE	Day 1: 0.08[a] Day 2: 0.12[a] Day 3: 0.02	Day 1: 0.1 (single starting dose)[a] Day 2: 0.05 Day 3: 0.05 Day 4: 0.05	Day 1: 0.02	Day 1: 0.03 Day 2: 0.025 Day 3: 0.025	Day 1: 0.06[a] Day 2: 0.04
Type of administration	Oral	IV	IV	Oral/IV	Oral/IV
Probability AE	Probable	Definite	Possible	Probable	Possible
PRISM score	0	21	4	18	23

F female, *NMS* neurologic malignant syndrome
[a] Daily dose higher then advised by the Dutch guidelines

dose–response studies are needed to optimize efficacy and safety of haloperidol for the treatment of PD.

Conflicts of interest The authors declare that they have no conflict of interest.

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