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Additional use of methotrimeprazine for treating refractory agitation in pediatric patients

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Dear Editor,

Refractory agitation (RA) is a frequent and challenging problem in patients in the pediatric intensive care unit (PICU). After exclusion of imminent hypoxia, the differential diagnosis of RA includes: (i) delirium due to the underlying critical illness, and/or (ii) withdrawal, and/or (iii) disinhibition/paradoxical arousal due to benzodiazepines [1, 2]. In most cases, haloperidol gives satisfactory results [3], although RA may persist despite this treatment. Also benzodiazepines are often given, but may be ineffective or even contraindicated to restore patient comfort. After all, many patients in a PICU already receive or have received benzodiazepines and may have developed a certain level of tolerance. In others, benzodiazepines should be avoided because of associated disinhibition, which has particularly been observed in critically and/or terminally ill children [2]. Therefore, a rescue strategy may be needed [1].

A possible solution for the treatment of RA is the addition of methotrimeprazine (MTZ, also known as levomepromazine or Nozinan), an aliphatic phenothiazine neuroleptic drug with a weak antipsychotic, but strong sedative effect. This classic neuroleptic is commonly used as co-medication in emergency psychiatry in adults to treat acute psychosis or mania by reducing levels of agitation, anger, and aggressiveness [4], thereby improving comfort for all—the patient, family, and members of the multidisciplinary team. There is no literature to allow for advisory dosages of MTZ in children with RA; however, in palliative care 0.1 mg/kg IV/SC/8 h is suggested [1]. In adults, maximum dosages of t.i.d. 25–50 mg/orally/24 h MTZ are common. Potential, but rare side effects of MTZ include tardive dyskinesia, akathisia, neuroleptic malignant syndrome, and extrapyramidal and cholinergically mediated side effects; a contraindication is bone marrow depression [4].

We recently used MTZ in four critically ill children presenting with RA (patient characteristics are summarized in Table 1). All patients initially received standard analgosedative treatment according to consensus guidelines [5]. Two patients developed delirium for which an individually titrated dosage of haloperidol remained insufficient or ineffective. A third patient suffered from therapy-resistant agitation during slowly weaning from sedation, for which several analgosedatives were

Table 1 Patient characteristics

Patient no.	Gender	Age (years)	Weight (kg)	Mortality	Medical condition	PIM score	PRISM score	Initial therapy for RA	Maximum rescue dosage methotrimeprazine
1	Male	13	62	No	Reduced consciousness caused by increased intracranial pressure, due to pilocytic astrocytoma in the third ventricle	1.91	1.73	Haloperidol	b.i.d. 6.25 mg orally
2	Male	5	19	No	Postoperative closing tracheostomy	1.12	1.12	Haloperidol	t.i.d. 1 mg intravenously
3	Male	15	20[a]	Yes	Respiratory insufficiency due to a swollen tongue	17.14	0.42	Haloperidol Ketamine Benzodiazepines Alimemazine Apomorphine Chloral hydrate	b.i.d. 10 mg enterally
4	Female	0.7	6.8	Yes	Respiratory insufficiency due to pulmonary hypertension	3.97	6.08	Haloperidol Ketamine Benzodiazepines Alimemazine	q.i.d. 1 mg intravenously

[a] Low body weight due to severe mental retardation and bedridden state based on pontocerebellar hypoplasia type 2

unsatisfactorily given. The last patient experienced repeated periods of agitation due to progressive pulmonary hypertension, for which amongst others haloperidol seemed ineffective. In all cases, additional intravenous or enteral administered MTZ successfully reduced RA and restored the comfort of the child and everyone involved. No side effects were observed. Long-term outcome of our four patients varied: patients 3 and 4 were treated with MTZ in the terminal phase of palliative care and died peacefully, patient 2 did not experience further agitation after treatment, and patient 1 still receives MTZ successfully.

We conclude that once RA still continues after adequate 24-h dosages of D2-blocking agents, the addition of MTZ by trial and error titration might be a useful option [4]. We would like to reintroduce and underscore, on the basis of empirical evidence and by analogy to what is known in adults [1, 4], the use and effectiveness of MTZ in the treatment of RA in critically ill children in the PICU.

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