Subgroup analysis of the extended efficacy and safety of low-dose methoxyflurane analgesia in adolescent patients from the STOP! study with acute trauma pain

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BACKGROUND AND GOAL OF STUDY

- Low-dose methoxyflurane, self-administered by the patient via a handheld inhaler (Pentrox[®], 3 mL dose) is a fast-acting, non-narcotic analgesic agent that has been used in Australia and New Zealand for over 40 years.
- Despite a large volume of published literature supporting the efficacy and safety of methoxyflurane at analgesic concentrations¹, previous studies have been mostly observational and uncontrolled.
- The STOP! study^{2,3} was a large double-blind, randomised, placebo-controlled UK study that investigated the efficacy and safety of low-dose methoxyflurane analgesia administered via the Pentrox[®] inhaler for the treatment of moderate to severe trauma pain in the Emergency Department (ED).
- The reduction in visual analogue scale (VAS) pain intensity in the first 20 minutes after the start of treatment has previously been reported^{2,3}. We present a post hoc analysis of the change from baseline in VAS pain intensity beyond this time point, and safety results, in a subgroup of adolescent patients aged 12 to 17 years (N=95).

MATERIAL AND METHODS

- 300 adult and adolescent patients aged ≥12 years presenting to the ED with acute trauma pain were randomised (at triage) in a 1:1 ratio to receive methoxyflurane (up to 2 x 3 mL) or placebo (normal saline), each via a Pentrox[®] inhaler.
- To maintain the blind, a drop of methoxyflurane was placed on the outside of the primed inhalers so that the smell between active and placebo treatments was indistinguishable.
- Study medication was self-administered by the patient by inhaling from the device as required while in the ED. Rescue medication (paracetamol/opioids) was available immediately upon request of the patient.
- VAS pain intensity was measured using the Painlog[™] 100 mm VAS (Schlenker Enterprises, Ltd., Lombard, IL., USA) at baseline and 5, 10, 15, 20 and 30 minutes after the start of inhalation of study medication, and every 30 minutes thereafter until rescue medication was administered or discharge from the ED, whichever was sooner.
- The primary efficacy endpoint was the change in VAS pain intensity score from baseline over the 20 minutes after the start of study medication inhalation. We present change from baseline in VAS pain intensity scores beyond 20 minutes after the start of treatment for the adolescent subgroup.
- Adverse events (not related to the trauma presentation) were recorded from enrolment until discharge, and at safety follow up (Day 14±2). Treatment-emergent adverse events (TEAEs) were summarised for the adolescent subgroup.

RESULTS AND DISCUSSION

Patient Characteristics

- The adolescent subgroup included 67 male patients and 28 female patients with a mean age of 14 years.
- A summary of injury type and site is presented in [Table 1](#). Most patients had injuries involving the limbs and categorised as “other” (predominantly sprains, soft tissue injury and muscular pain).

Table 1. Injury Details (Adolescent Subgroup)

NUMBER (%) OF PATIENTS		METHOXYFLURANE (N=47)	PLACEBO (N=48)	TOTAL (N=95)
Injury site	Back	1 (2.1)	1 (2.1)	2 (2.1)
	Face	2 (4.3)	1 (2.1)	3 (3.2)
	Left lower limb	5 (10.6)	9 (18.8)	14 (14.7)
	Left upper limb	13 (27.7)	8 (16.7)	21 (22.1)
	Other	7 (14.9)	4 (8.3)	11 (11.6)
	Right lower limb	6 (12.8)	11 (22.9)	17 (17.9)
	Right upper limb	13 (27.7)	14 (29.2)	27 (28.4)
Injury type	Contusion	9 (19.1)	6 (12.5)	15 (15.8)
	Dislocation	1 (2.1)	1 (2.1)	2 (2.1)
	Fracture	11 (23.4)	11 (22.9)	22 (23.2)
	Injury due to foreign body	1 (2.1)	-	1 (1.1)
	Laceration	1 (2.1)	1 (2.1)	2 (2.1)
	Other [†]	24 (51.1)	29 (60.4)	53 (55.8)

* “Other” injury types were predominantly sprains, soft tissue injury and muscular pain.
Note: First injury details are presented. Only one patient had more than one injury.

- Baseline pain severity is presented in [Table 2](#). Almost half of the patients (46%) in the adolescent subgroup had severe pain (NRS score of 7) at baseline. All remaining patients had moderate pain at baseline (NRS score of 4 to 6).

Table 2 Numeric Rating Scale (NRS) Pain Score at Baseline (Adolescent Subgroup)

BASELINE NRS PAIN SCORE	METHOXYFLURANE (N=47) n (%)	PLACEBO (N=48) n (%)	TOTAL (N=95) n (%)
4	4 (8.5)	4 (8.3)	8 (8.4)
5	7 (14.9)	14 (29.2)	21 (22.1)
6	15 (31.9)	7 (14.6)	22 (23.2)
7	21 (44.7)	23 (47.9)	44 (46.3)

Note: A score of 4 to 7 (on the 11-point NRS) was required for study eligibility.

- Mean (±standard deviation) VAS pain scores at baseline were 61.7 ±16.56 mm in the methoxyflurane group and 61.0 ±13.33 mm in the placebo group.

VAS pain intensity beyond 20 minutes

- Mean change in VAS pain intensity from baseline over the first 20 minutes was significantly greater for the methoxyflurane group than the placebo group (previously reported data for the overall population² and adult subgroup³).
- The decrease in VAS pain intensity achieved with methoxyflurane over the first 20 minutes was maintained beyond 20 minutes after the start of treatment in adolescent patients who continued to have VAS pain intensity measurements recorded ([Figure 1](#)).

Figure 1. Mean Change from Baseline in Visual Analogue Scale (VAS) Pain Intensity Scores ≥20 Minutes After the Start of Treatment (Adolescent Subgroup)

- The number of patients with available VAS data decreased at each time point, which was mainly due to discharge of patients from the ED or start of a planned ED procedure.

Safety

- TEAE rates for the adolescent subgroup are presented in [Table 3](#). Fifty-five AEs were reported by 24 patients (51%) in the methoxyflurane group and 35 AEs were reported by 20 patients (42%) in the placebo group.

Table 3 Adverse Events (Adolescent Subgroup)

NUMBER (%) OF PATIENTS	METHOXYFLURANE (N=47)	PLACEBO (N=48)
TEAEs	24 (51.1)	20 (41.7)
Treatment-related TEAEs	11 (23.4)	5 (10.4)
Serious TEAEs	0	0
TEAEs leading to withdrawal	2 (4.3)	2 (4.2)
TEAEs reported by ≥3 patients in either treatment group		
Headache	12 (25.5)	11 (22.9)
Dizziness	7 (14.9)	1 (2.1)
Somnolence	3 (6.4)	0
Influenza like illness	0	3 (6.3)

TEAE = treatment-emergent adverse event.

- The TEAEs reported were generally mild and transient in nature.
- The most commonly reported TEAEs were headache, dizziness, somnolence and influenza type illness. Dizziness and somnolence were more common in methoxyflurane-treated patients, influenza type illness was more common in placebo-treated patients and headache was reported at a similar frequency in both groups.
- No serious TEAEs were reported.
- Two patients (4%) in each treatment group withdrew due to a TEAE:
 - Methoxyflurane group: one patient due to feeling dizzy and one patient due to light headedness, bad taste and burning in his mouth.
 - Placebo group: one patient due to feeling light headed and nausea and one patient due to loss of consciousness lasting for ~1 minute.
- All TEAEs leading to withdrawal resolved on the same day.

CONCLUSION

- These results show that the reduction in pain intensity with low-dose methoxyflurane analgesia is maintained for the duration of use in adolescent patients with acute trauma pain.

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