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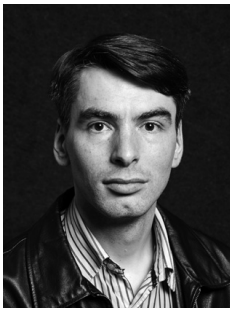
Evaluation of methoxyflurane (Penthrox®) efficacity for acute traumatic pain relief: a pilot study



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Summary

This prospective, descriptive, non-randomized study included 20 patients and presents results of methoxyflurane's (Penthrox®) analgesic efficiency tests for acute traumatic pain relief. Penthrox® reduced intensity of acute pain by 68% (95CI 52-84%) and anxiety by 73% (95CI 63-83%) in comparison with initial values (before inhalation). Clinical efficiency of Penthrox® with the aim of acute pain relief had a NNT of 2,5, being comparable with that of morphine (NNT=3,6) and better than that of tramadol (NNT=5,5). Penthrox® clinical effects satisfied 70% patients. The side pharmacological effects (good mood, dizziness, drowsiness, nausea, logorrhea), which were observed in 85% patients, had no significant negative impact. *Anestezjologia i Ratownictwo 2010; 4: 99-103.*

Keywords: acute pain, analgesia, methoxyflurane

Introduction

Effective and safe relief of acute pain is not only an important medical problem. Since 2004, pain relief is one of the fundamental human rights [1]. None of available today analgesics has the desired efficiency and is without adverse effects [2]. For example, use of nitrous oxide requires expensive equipment and highly qualified medical staff. Combination opioid/benzodiazepine requires the presence of peripheral venous access to ensure security, and appropriate dose titration of analgesia or sedation are relatively difficult. Ketamine is associated with long recovery time and propofol – with respiratory depression. Intravenous regional analgesia requires the presence of a specialized equipment and specialized potential of expertise [3].

One of the possible solutions to the problem of efficient and secure acute pain relief could be analgesic efficiency testing of some drugs within a new frame of indications, drugs used in the past for general anaesthesia. With the exception of nitrous oxide, methoxyflurane (Penthrox®) is the only volatile analgesic, currently available outside the operating room.

For this reason, evaluation of analgesic effectiveness, safety and patient's satisfaction, with specifying the possible indications and determining areas of

Penthrox®'s application need to be evaluated in light of new knowledge and perspectives.

Therefore, we proposed a pilot-study intended to quantify Penthrox® effects in severe acute traumatic pain.

Material and methods

- **Design of study**

This prospective, descriptive, non-randomized pilot study was performed at the National Scientific and Practical Centre for Emergency Medicine. The Ethics Committee of the institution approved the study protocol. Inclusion criteria in the study were: adult (≥18 years) with severe pain (≥50 mm on visual analogue score, VAS) of traumatic origin, who had not previously received another analgesic and who gave informed consent to participate in study. Exclusion criteria were based on the presence of contraindications to methoxyflurane administration, such as, for example, kidney or liver disease, diabetes, coma, hemodynamic instability, or patient's refusal to participate in the study.

➢ *Methoxyflurane (Penthrox®) administration*

Methoxyflurane was used by the patient by inhalation through the inhaler Penthrox® (Figure 1), after a prior brief training. Inhaler, loaded with 3 mL of methoxyflurane, produces a vapour concentration of 0,1-0,2% (when the dilution orifice is open) or 0,3-0,4% (the dilution orifice is closed). Full pharmacological effect establishes after 8-10 deep inspirations.

Figure 1. Penthrox® inhaler and a 3 mL phial of methoxyflurane

- **Data Acquisition**

General parameters (age, body weight, height) and study specific parameters were recorded. In this context, VAS was used to assess pain intensity and anxiety degree prior to analgesia, during inhalation, immediately after inhalation was finished and more than 45 minutes from the end of Penthrox®'s administration. Patient's satisfaction was assessed using Likert Score of 5 points (very satisfied, satisfied, indifferent, unsatisfied, very unsatisfied).

The following situations were defined as severe adverse events: acrocyanosis, apnoea, stridor, laryngospasm, upper airway obstruction, bronchospasm, unstable haemodynamics, paradoxical reactions, pulmonary aspiration, regurgitation, need to intubate trachea, permanent neurological damage.

- **Data analysis**

Data were filled in Excel tables, version 2007 (Microsoft®, USA). Statistical analysis was performed with GraphPad Prism® software, version 4.1 (GraphPad Software, San Diego, California, USA). For statistical analysis of parameters with continuous values ANOVA test was used. For the number of 20 persons, included in our study, which generated 4 columns of data, a critical value of test F ≥3,13 allows to identify significant statistical differences with a probability of 95%. Critical value for F was obtained from standardized statistical tables. In case of obtaining a F ≥3,13, the magnitude of obtained difference was calculated by applying the Bonferroni's post-test of significanc,, where a p≤0,05 was considered significant. Results are presented as mean values. In cases considered as relevant, 95% confidence intervals (95CI) were added.

Quantifying clinical effectiveness of Penthrox® was reflected by using NNT indicator (*number need to treat*), which represents the number of patients that must be treated to see the expression of the desired clinical effect of the drug in question. To calculate the NNT, as cut-off value of effective/ineffective the reduction of pain intensity by VAS score ≥50% from baseline was considered.

Results

The study included 20 patients, 12 men and 8 women, with a mean age of 42,7 (95CI 34,3-51) years, an average body weight of 70,7 (95CI 66,5-74,8) kg and an average height of 170 (95CI 166-173) cm. Causes of acute pain were: upper limb joint dislocation – 7 (35%) cases, malleolar fracture – 4 (20%) cases, painful medical procedures – 4 (20%) cases, transportation of the traumatized patient within the hospital – 3 (15%) cases, acute lowerback pain – 2 (10%) cases. The analgesic effect obtained by self-administered Penthrox® is presented in Figure 2. An average reduction of 68% (52-84% 95CI) of pain intensity from baseline (before inhalation of Penthrox®) was found.

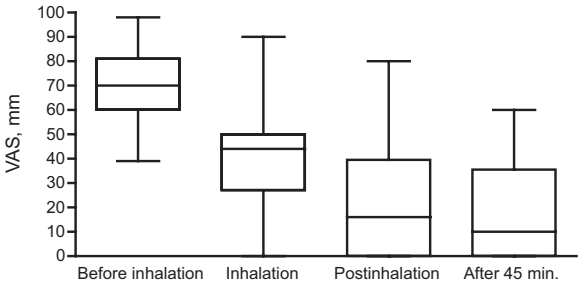

Figure 2. The analgesic effect of methoxyflurane for acute pain relief

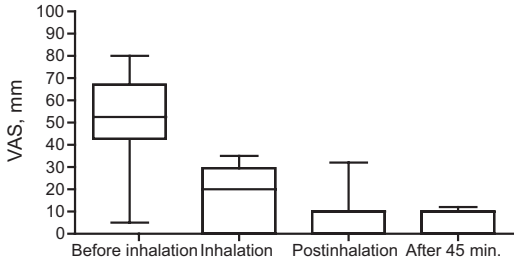

Figure 3. Anxiolytic effect of methoxyflurane for acute traumatic pain relief

Decreased pain intensity according to the stages of data acquisition and statistical significance of this phenomenon were reproduced in terms of Bonferroni's post-test in Table 1.

The anxiolytic effect obtained by self-administered methoxyflurane is shown in Figure 3. Patient's anxiety decreased with 73% (63-83% 95CI) from baseline.

The degree of anxiolysis, according to the stages of data acquisition and statistical significance of the effect are reproduced in terms of Bonferroni's post-test in Table 2.

Penthrox® clinical effectiveness, reflected in terms of NNT indicator, in our study was 2,5. Comparative analysis of data obtained with those found in the

Table 1. Magnitude of decrease in pain intensity in case of analgesia with methoxyflurane

Columns of values	The differences between average values	F	p	95% CI of the average differences
Before inhalation vs. inhalation	31, 0	7,0	<0,001	18,9 – 43,3
Before inhalation vs postinhalation	47,6	10,7	0,001	35,4 – 59,8
Before inhalation vs after 45 min.	53,8	12,1	0,001	41,6 – 66,0
Inhalation vs postinhalation	16,5	3,7	0,01	4,3 – 28,7
Inhalation vs after 45 min.	22,8	5,1	0,001	10,6 – 35,0
Postinhalation vs after 45 min.	6,3	1,4	ns	-5,93 – 18,5

Table 2. Anxiolysis obtained under analgesia with methoxyflurane

Columns of values	The difference between average values	F	p	95% CI of the average differences
Preinhalation vs inhalation	33,6	7,9	<0,001	22,0 – 45,1
Preinhalation vs postinhalation	43,7	10,2	<0,001	32,0 – 55,3
Preinhalation vs after 45 min.	45,2	10,6	<0,001	33,6 – 56,8
Inhalation vs postinhalation	10,1	2,3	ns	-1,8 – 22,0
Inhalation vs after 45 min.	11,7	2,7	ns	-0,2 – 23,6
Postinhalation vs after 45 min.	1,6	0,4	ns	-10,3 – 13,5

Table 3. Comparative analysis of some analgesics with Penthrox clinical effectiveness in terms of NNT

Drug	The average value of NNT	Nr. of studed patients
Etoricoxib 180 mg per os	1,4	123
Ibuprofen 400 mg per os	2,9	101
Ibuprofen 200 mg per os	3,0	1414
Morphin 10 mg i.m.	3,4	946
Paracetamol 1000 mg per os	4,2	2759
Aspirin 600 mg per os	4,9	5061
Tramadol 100 mg per os	5,5	882
Methoxyflurane (Penthrox) 0,2-0,4%	**2,5**	**20**

literature [4] for other analgesics is shown in Table 3.

Patient satisfaction, expressed by Likert score is shown in Figure 4.

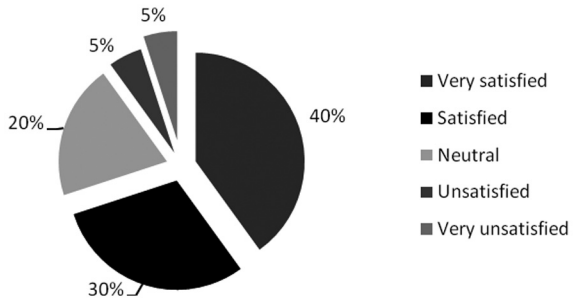

Figure 4. Degree of patient's satisfaction regarding clinical effectiveness of methoxyflurane

Thus, 70% of patients felt satisfied with Penthrox® effectiveness in acute traumatic pain relief. One patient expressed himself as "totally unsatisfied" because she had nausea during drug inhalation and she requested to change the analgesic. In the second patient, who expressed as being "unsatisfied", the analgesic effect of methoxyflurane was not sufficient to relief pain during malleolar fracture reduction, and necessitated administration of an opioid analgesic (fentanyl).

No significant changes were observed clinically or statistically among the values of blood pressure, heart rate, respiratory rate and sedation level during or after methoxyflurane inhalation. No severe adverse events, as, mentioned in the above list, were noted. Pharmacological side effects, not necessarily being negative and considered clinically insignificant, were present in 85% of patients: good mood in 14 (70%) patients, dizziness – in 13 (65%) patients, drowsiness – in 6 (30%) patients, nausea – in 1 (5%) patient and logorrhea – in 1 (5%) patient.

Discussion

There are few contemporary publications describing the analgesic effectiveness of Penthrox®. Babl F. and co. (2006), in a study performed on a group of 105 paediatric patients, reported a 34% reduction of acute pain intensity, treated at pre-hospital stage [5]. Buntine P. and co-authors (2007) reported in adult patients 24-32% reduction of the acute pain intensity in the same conditions [6]. Our data (reduction of pain intensity by 68%; 95CI 52-84%) indicate a doubled magnitude of analgesic effect in comparison with the quoted above. These differences could be probably explained by socio-cultural differences between Australian and Republic of Moldova's population, also by using Penthrox® in other indications than those, which were compared with data or by comparatively small number of patients included in our study.

Index NNT of 2,5 places methoxyflurane at the level of morphine (NNT 3,4), far outmatching tramadol (NNT 5,5) – the only comparable drugs, for the acute traumatic pain relief.

Observed in our study more gradual pattern of analgesic in comparison with the anxiolytic effect can be explained by the fact that the start of medical procedures inhibits the phenomenon of events' anticipating, produced by cortex and, respectively, the degree of anxiety. To the contrary, nociceptive influx, augmented by medical procedures, counterbalances the analgesic effect of the drug, reached highest level after the surgery.

Satisfaction rate of 70% in our study is comparable to that reported in a meta-analysis of Grindlay and Babl (2009) – 94% of patients and 74% of nurses were satisfied with the effect [7].

Although the nephrotoxic effect of methoxyflurane was not part of our research, this aspect was almost always mentioned by the doctors who took care of patients in our study. After a break of about 30 years, when it was removed from the arsenal of anaesthesia because of its nephrotoxic effect, methoxyflurane (Penthrox®) gets back on the global market as an analgesic for acute pain relief. Short durations of administration and significantly lower doses of methoxyflurane (Penthrox®), required to relief pain, avoid nephrotoxic effect, which is dependent on the dose and duration of exposure. To produce a subclinical nephrotoxic effect in adult patient requires a dose of 20-24 g (96 mL) of methoxyflurane in comparison to maximal dose for 24 hours of 1,5g (6 mL), recommended and used today [7].

Conclusions

1. Penthrox® reduced acute pain intensity by 68% (52-84%; 95CI) from baseline (before inhalation).
2. Penthrox® reduced anxiety by 73% (63-83%; 95CI) from baseline (before inhalation).
3. Clinical effectiveness of Penthrox® for acute pain relief is comparable to that of morphine and better

than that of tramadol (NNT respectively 2,5 vs. 3,4 vs. 5,5), achieving a patient's satisfaction level of 70 %.

4. Pharmacological side effects (good mood, dizziness, drowsiness, nausea, and logorrhea), recorded in 85% of patients, had no significant negative impact.

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Piśmiennictwo

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