

MAC-SPARING EFFECT OF TRANSDERMAL FENTANYL IN SEVOFLURANE-ANESTHETIZED SHEEP

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(Received 30 January, Accepted 26 April 2018)

Transdermal fentanyl allows for consistent plasma concentrations of a potent synthetic μ -opioid receptor agonist and can provide constant post-operative analgesia for up to 72 h. The aim of this study was to determine the reduction of the minimum alveolar concentration of sevoflurane (MAC_{SEVO}) by transdermal fentanyl in non-pregnant ewes. Nine sheep were mask induced with sevoflurane (SEVO in oxygen). MAC_{SEVO} determinations involved electrical current applied to the lateral metacarpus as a supramaximal stimulus and measurements in duplicate. Seven days later, a fentanyl patch (75 μ g/h) was applied to each sheep and 15.1 \pm 1.8 h later the MAC re-determined (MAC_{SF}). MAC_{SF} was 1.99 \pm 0.32 %, corresponding to 25.6 \pm 8.1 % reduction from MAC_{SEVO} ($P < 0.001$). Transdermal fentanyl produces a significant MAC_{SEVO} -sparing effect with minimal effect on cardiovascular parameters.

Key words: Minimum alveolar concentration (MAC); sevoflurane; sheep; transdermal fentanyl

INTRODUCTION

Fentanyl is a potent synthetic μ -opioid receptor agonist and commonly used analgesic in clinical veterinary practice and research settings. As humane treatment of research animals receives increasingly more attention, evaluation of treatment strategies for intra- and post-operative pain is an important subject of research interest. Transdermal administration of fentanyl, via a fentanyl patch, allows for more consistent plasma concentrations for up to 72 h compared to these of intermittent boluses of various analgesic medications [1, 2]. Systemic opioids provide intra-operative antinociception, which may result in variable reduction of the minimum alveolar concentration (MAC) of inhalant anesthetics, such as sevoflurane (SEVO). We hypothesized that the administration of transdermal fentanyl will significantly reduce MAC_{SEVO} in sheep and serve as a valuable anesthetic adjunct as has been shown in other species [3, 4].

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MATERIAL AND METHODS

Nine female non-pregnant Sardinian milk sheep, aged 5 (range 3-10) years and weighing mean (\pm SD) 34.0 (\pm 3.7) kg, determined to be healthy by physical examination, hematology and serum chemistry results (data not presented), were enrolled and anesthetized twice, seven days apart. The study protocol was approved by the Institutional Animal Care and Use Committee at the University of Sassari (CIBASA; protocol number 23/052) according to Italian legislation and is compliant with all relevant national regulations and institutional policies for the care and use of animals.

The sheep were purchased from local farmers for whom each sheep's milk production span had ceased. The herd was housed collectively in an outdoor pen that provided protection from the elements by a large run-in shed. Water and hay were provided ad libitum except during standard pre-anesthetic food withdrawal times (accomplished via a mesh muzzle). All sheep were allowed a minimum two week acclimatization period between acquisition of sheep and initiation of experimental procedures. Upon completion of the study, all sheep were allowed free access to a grassed pasture and maintained as property of the University of Sassari.

Initial determinations of MAC_{SEVO} in these sheep were part of an original SEVO MAC study [5]. Briefly, animals were face-mask induced with SEVO in O_2 and immediately mechanically ventilated. MAC_{SEVO} was determined in duplicate via a modified "up-down" protocol [6] that involved as a supramaximal noxious stimulus an electrical current (5 Hz/1 ms/50 mA) delivered to the lateral metacarpus for 60 s or until gross purposeful movement was observed.

Seven days after initial experiments, the skin surface over the medial aspect of the antebrachium was clipped, thoroughly cleaned with an antiseptic solution, and allowed to dry prior to application of a transdermal fentanyl patch (Duragesic, Janssen Pharmaceuticals; 75 μ g/h). The patch was secured in place with an auto-adhesive bandage. After a mean of 15.1 (\pm 1.8) h post patch application, animals were re-anesthetized for MAC_{SEVO} determination, again in duplicate, in the presence of fentanyl (MAC_{SP}) employing the same protocol as in the original MAC study.

Given that the scientific idea behind this study was original and no similar studies have been carried out in the past in this species with fentanyl patches and sevoflurane, there was no possibility of generating a list of feasible statistical assumptions based on previous scientific evidence. Therefore, the computation of an appropriate sample size could not be performed a priori. Thus, at the end of the study a post-hoc power calculation was informally carried out to confirm inclusion of at least eight sheep for this study, in which a two-tailed t-test with power of 0.98, and an alpha error of 0.05 was applied.

All variables were tested for normal distribution by a Shapiro-Wilk test. Parametric data are reported as mean (standard deviation, \pm SD) and non-parametric data are reported as median (interquartile range, IQR). Student's t test and Wilcoxon Signed-

Rank test were employed for parametric and nonparametric data sets, respectively to detect statistically significant differences between groups. A two-tailed P -value < 0.05 was accepted as indicating statistically significant differences.

RESULTS AND DISCUSSION

The mean fentanyl dose in each sheep was $2.2 (\pm 0.28)$ $\mu\text{g}/\text{kg}/\text{h}$. The MAC_{SEVO} as determined previously in this study group was $2.67 (\pm 0.30)$ %. The measured MAC_{SF} was $1.99 (\pm 0.32)$ % and thus on average $25.6 (\pm 8.1)$ % lower than MAC_{SEVO} ($P < 0.001$). The mean heart rate recorded during MAC_{SF} determinations (113 beats/min) was significantly higher than during MAC_{SEVO} measurements (107 beats/min), $P = 0.008$. Similarly, the end tidal CO_2 partial pressure was higher in MAC_{SEVO} (43 mmHg) compared to MAC_{SF} (41 mmHg) ($P < 0.001$). Invasive blood pressure recordings, temperature, or respiratory rate were not statistically different between groups. All sheep recovered smoothly upon discontinuation of SEVO administration.

The results of the current study confirm our hypothesis that transdermal fentanyl results in a marked reduction (25.6 %) of MAC_{SEVO} in non-pregnant adult sheep, 15 h after patch application without compromising cardiopulmonary function during anesthesia, as the differences observed in HR and ETCO_2 between groups were clinically irrelevant despite statistical significance. Such a MAC-sparing effect parallels the reduction of isoflurane MAC measured in dogs (36.6 %) [3] and in cats (18 %) [4] with transdermal fentanyl and also in isoflurane-anesthetized goats during intravenous fentanyl infusion, where a 0.005 mg/kg loading dose followed by 0.005 mg/kg/h produced a 27.6 % MAC reduction [7]. While two studies have evaluated post-operative pain scores after transdermal fentanyl application in sheep [8, 9], this is the first one in sheep demonstrating an anesthetic-sparing effect of fentanyl when delivered by this route.

In comparison to studies examining MAC-sparing effects of other full μ -agonists, the magnitude of MAC reduction reported here is larger than that found with hydromorphone (7.6 %) or oxymorphone (12.4 %) in desflurane-anesthetized sheep [10], but similar to that observed after i.v. morphine (2 mg/kg) administration in goats (29.7 %) [11]. The variability in MAC-sparing effects may very well be the result of improper opioid dosing leading to plasma concentrations that are not equal in their efficacy of eliciting antinociception. Not surprisingly, Dziki et al. demonstrated a greater MAC-sparing effect with increasing infusion rates and hence plasma levels of fentanyl [7].

The mean fentanyl dose in the current study was $2.2 \mu\text{g}/\text{kg}/\text{h}$, which - based on pharmacokinetic studies of transdermal fentanyl patches in sheep - likely resulted in mean serum fentanyl concentrations of approximately 1 ng/mL at 15 h after application [1,9]. However, a review of transdermal opioids in humans emphasizes the difficulty in assigning a firm concentration-effect relationship to fentanyl, as the

effective plasma concentration depends on various factors including pain intensity, opioid receptor expression, nociceptive impulse traffic, and others [2]. Additionally, trans-dermally administered fentanyl is subject to variable absorption due to differences in skin thickness, body surface temperature, and application technique [1]. Although Yackey et al. aimed to compare a dose-response effect on isoflurane MAC-reduction with transdermal fentanyl (25 µg/h versus 50 µg/h fentanyl patches) in cats, no difference was observed between study groups with respect to MAC-reduction nor in fentanyl plasma concentrations [4]. Therefore, future studies examining the plasma concentration-dependency of MAC-reduction after transdermal fentanyl in sheep are warranted.

In summary, the current study demonstrates that transdermal fentanyl results in a significant MAC-sparing effect and is well tolerated as an adjunctive agent in SEVO anesthetized sheep.

Acknowledgements

This work was supported by the Fondazione Banco di Sardegna and the Regione Autonoma della Sardegna, Italy and the University of Sassari [Protocol n. 4357] as well as intramural funding of the Section of Anesthesia at University of Pennsylvania, School of Veterinary Medicine. The authors thank Professor Bernd Driessen, University of Pennsylvania, Department of Clinical Studies-New Bolton Center for his advice and support during experimentation and preparation of the present manuscript. The authors thank Dr. Denis Novak, president of the Serbian Association of Small Animal Practitioners (SASAP), for the translation of the summary into Serbian.

Authors' contributions

LD performed manuscript preparation, review & editing, data analysis. ESP funding acquisition, project administration. AS study design, investigation. NC funding acquisition, conceptualization, methodology, investigation. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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EFEKAT TRANSDERMALNOG FENTANILA NA SMANJENJE MAC KOD OVACA ANESTEZIRANIH SEVOFLURANOM

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Transdermalni fentanil omogućava stalnu koncentraciju u plazmi potentnog sintetičkog agoniste μ -opioidnih receptora i može da obezbedi konstantnu post-operativnu analgeziju do 72h. Svrha ove studije je bila da odredi smanjenje minimalne alveolarne koncentracije sevoflurana (MAC_{SEVO}) upotrebom transdermalnog fentanila kod negravidnih ovaca.

Devet ovaca je indukovano preko maske sa SEVO u kiseoniku. Određivanje MAC_{SEVO} vršeno je aplikacijom električne struje na lateralni metakarpus kao supramaksimalni

stimulus i to duplim merenjima. Sedam dana kasnije, fentanil flaster (75 µg/h) je aplikovan svakoj ovci i nakon $15,1 \pm 1,8$ h je ponovno određivan MAC (MAC_{SF}). MAC_{SF} je bio $1,99 \pm 0,32$ %, što je odgovaralo $25,6 \pm 8,1$ % smanjenju u odnosu na MAC_{SEVO} ($P < 0,001$). Transdermalni fentanil omogućava značajno smanjenje MAC_{SEVO} - (efekat uštede) sa minimalnim uticajem na kardiovaskularne parametre.