Butorphanol induces anxiety-like behaviour and distress in piglets

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Butorphanol führt zu ängstlichem Verhalten und Stressreaktionen bei Ferkeln

In einer früheren Studie zur Schweinekastration unter Isoflurananästhesie mit Butorphanol Prämedikation wurden schwerwiegende Nebenwirkungen festgestellt. Da dies bei Schweinen bisher nicht berichtet wurde, untersuchten wir die Wirkung von Butorphanol bei Ferkeln. In dieser verblindeten Studie wurden zehn 27 Tage alte Ferkel zufällig den Studiengruppen zugeteilt, um entweder 0,2 mg/kg Butorphanol (Gruppe B) oder 0,9% Kochsalzlösung (Kontrollgruppe C) intramuskulär zu erhalten. Ihr Verhalten wurde 60 Minuten lang von zwei unabhängigen Beobachtern auf Videoaufnahmen bewertet.

Zwei bis 15 Minuten nach der Anwendung zeigten die Ferkel der Gruppe B Unruhe, Stress und übermässige Lautäusserungen. Die Bewegungsaktivität war während der ersten 40 Minuten im Vergleich zu Gruppe C erhöht. Die Ferkel der Gruppe C schliefen die meiste Zeit des Versuchs (45,1 ± 2,9 Minuten Gruppe C vs 12,7 ± 2,9 Minuten Gruppe B, $p < 0{,}0001$). Nach Butorphanol Applikation zeigten die Schweine Sprünge gegen die Wände (im Mittel: 1,2 Sprünge/Minute in den ersten 30 Minuten in Gruppe B gegenüber 0 Sprünge/Minute in Gruppe C, $p = 0{,}0011$). In Gruppe B drückte ein Tier seinen Kopf gegen die Wand und vier Tiere zeigten starkes Hecheln und Keuchen. Dreißig Minuten nach der Butorphanol-Anwendung wurden die Ferkel hyperthermisch (41,0 ± 0,7 °C Gruppe B vs 39,6 ± 0,3 °C Gruppe C, $p = 0{,}0075$).

Die Ergebnisse dieser Studie zeigen, dass 0,2 mg/kg Butorphanol intramuskulär bei schmerzfreien Ferkeln schwere Nebenwirkungen hervorruft, die vergleichbar sind mit denjenigen, welche nach Verabreichung von Opioiden bei anderen Arten berichtet wurden.

Keywords: Ferkel, Anästhesie, Butorphanol, Nebenwirkung, Unruhe

Abstract

In a previous study that used butorphanol in pigs before castration performed under isoflurane anaesthesia, severe adverse effects were recorded. As in pigs, this has not been reported before, we aimed to investigate the effects of butorphanol in piglets. In this study ten 27 days old piglets were randomly allocated to receive either 0,2 mg/kg butorphanol (group B) or saline 0,9% (control group C) intramuscularly. Their behaviour was assessed for 60 minutes by two independent observers from videotapes.

Two to 15 minutes after application, piglets in group B showed restlessness, distress and excessive vocalisation. Locomotor activity was increased, the piglets laid down considerably less frequently ($p = 0{,}034$) and for shorter time periods ($p = 0{,}0014$) during the first 40 minutes compared to group C. Group C animals slept most time of the experiment (45,1 ± 2,9 minutes in group C vs 12,7 ± 2,9 minutes in group B, $p < 0{,}0001$). After receiving butorphanol, pigs showed jumping against the wall (mean 1,2 times per minute during the first 30 minutes in group B vs 0 times per minute in group C, $p = 0{,}0011$). In group B, one animal pressed its head against the wall and four animals showed severe panting and gasping. Thirty minutes after butorphanol application piglets became hyperthermic (41 ± 0,7 °C group B vs 39,6 ± 0,3 °C group C, $p = 0{,}0075$).

The results of this study show that 0,2 mg/kg butorphanol intramuscularly induces severe side effects in pain-free piglets that are similar to those reported following opioid administration in other species.

Schlüsselwörter: piglet, anaesthesia, butorphanol, side effect, restlessness

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Background

The number of potent analgesics that are registered to control castration related pain in piglets is very limited. Butorphanol, an opioid acting as a pure agonist at κ-opioid-receptors (KORs) could be a suitable drug to provide analgesia in pigs.[1] In farm animals it is the most frequently used opioid.[2] For cows and adult pigs, it has been shown that the addition of butorphanol to general anaesthesia regimes improves sedation and the quality of anaesthesia.[3–5] Therefore, butorphanol is often added to anaesthesia protocols for farm animals in order to enhance sedation, provide additional analgesia in anaesthetised animals or for postoperative analgesia.[2]

However, in an earlier inhouse study that aimed at improving analgesia for castration performed under inhalation anaesthesia in piglets, it was observed that the sole use of butorphanol before induction of anaesthesia might induce adverse reactions.[6] Cyanosis, salivation, vomiting, dyspnoea, excitations and paddling were noted after drug administration in five out of seven piglets.[6] Also with injectable anaesthesia protocols containing butorphanol (ketamine-azaperone-butorphanol) in piglets undergoing castration, jumping and excitations after administration of this drug mixture were observed, which could not be explained.[7]

To the knowledge of the authors, previous studies that used butorphanol in pigs in combination with sedatives or injectable anaesthetics[3, 5, 7, 9–12] never described the adverse effects observed by Hug et al.[6] Besides some excitations during induction of anaesthesia[7, 10] that were not attributed to butorphanol, no study mentioned behavioural side effects despite using 0,2 mg/kg butorphanol, probably as a result of heavy sedation caused by other concurrently used drugs.

The occurrence of such excitatory behaviour and behavioural changes has been described for cattle,[2] sheep,[2, 13, 14] and horses[15] and it typically has occured if butorphanol was administered to animals not in pain.

The goal of the present study was to observe in a randomized, sham treatment controlled, blinded trial the effects of intramuscular butorphanol alone in piglets not undergoing any other treatment.

The hypothesis was that an intramuscular dose of 0,2 mg/kg butorphanol induces excitatory behaviour similar to other species.

Material and methods

The experimental study conditions were random order of group allocation and blinded assessment.

To show with a power of 80% and an alpha error of 0,05 that butorphanol is responsible for the observed untoward effects (with an expected incidence of 75% compared to none in the control group) 10 piglets were included in the study. The test animals were 10 cross-breed (F1 Large White × Landrace) male piglets, age 27 days and weighing 8,5 ± 1,3 kg. They originated from 2 different litters (4 and 6 piglets, respectively) and were housed together with their mothers on a commercial farm in Switzerland. The piglets were weighed and temperature was checked daily. Based on the clinical examination the piglets were considered healthy. The piglets were randomly picked from their litters (first all 6 males from one litter and then another 4 from another litter) marked with a clearly visible number on the back (1–10) and weighed. Piglets were assigned either to the butorphanol (group B) or saline (control group C) group by drawing a lot from an envelope, containing five butorphanol and five saline lots.

The piglets undergoing the trial were placed together in a large stall, with solid wood walls of 1,4 meter height and wood chips flooring as in their normal stable box. The stall was equipped with a camcorder with wide angle lens, that filmed the whole area within the stall. After 10 minutes of acclimatization the piglets were videotaped for 10 minutes before drug administration and for another 60 minutes after drug administration.

Piglets were injected with 0,2 mg/kg butorphanol (Butomidor 10 mg/ml ad. us. vet., Streuli Pharma AG, Uznach, Switzerland) or an equal amount of saline 0,9% intramuscularly (IM) into the neck musculature according to the random assigned trial group.

Piglets behaviour was assessed retrospectively by two independent, blinded observers. The following behaviours were counted continuously and summed up each for a span of five minutes (min): Number of jumping against the walls (events) and lying down (events). Duration of lying in lateral recumbency and duration of sleeping (=laying in lateral recumbency with closed eyes) was also timed.

T0 was defined as the five minutes after butorphanol administration, T5 as the time span 5–10 minutes after drug administration, T10 time span from 10–15 minutes after drug administration and so on.

Every five minutes a score for intensity of panting (no panting=0; moderate panting=1; severe panting=2) and a score for vocalizations during the past five minutes was awarded (no screaming=0; moderate screaming=1; very loud screaming=2). The highest score observed in five minutes was awarded. Any other conspicuous behavior was noted.

After 30 minutes, rectal temperature was measured. Room temperature was 28 °C.

Statistical analysis was performed with help of R (R Foundation for Statistical Computing, Vienna, Austria) and Microsoft Excel 2016. Agreement between scorers was tested using Cohen's kappa coefficient.

Normality was tested by means of the Shapiro-Wilk test. For normally distributed data an independent samples t-test was used to compare the two groups and for non-parametric data a Mann-Whitney test. For repeated measures a Poisson regression Model was used with each piglet as random effect, group as a categorical independent variable, and the variable tested at each time point as the dependent variable. P-values $<$ 0,05 were considered to be significant.

Results

There was no significant difference between animals concerning body weight and treatments were equally distributed to litter affiliation.

Body temperature 30 min after injection was significantly different between group B and C (41,1 ± 0,7 °C vs 39,7 ± 0,3 °C, p = 0,0089).

Cohen's kappa coefficient (0,82) showed very good agreement between the two observers. Within 2 to 15 min after injection, piglets in group B showed restlessness and distress and started to jump against and up the walls for 20 to 40 minutes (significant different to group C between 5–40 minutes, p $<$ 0,0001). Except for one piglet in group C that jumped 5 times against the wall in the first 15 seconds after being put into the box and another one that showed the same behaviour after 40 minutes, group C piglets otherwise never jumped up the walls.

Four piglets of group B excessively scratched the litter with their muzzle, which was not recorded in the control group.

Butorphanol-treated piglets laid down less frequently and for shorter duration than control piglets. The frequency of lying down was significantly lower in group B compared to group C at T0, T15, T20 and T25 (0 ± 0,9 vs. 2 ± 2,2; 0,4 ± 0,9 vs. 4,0 ± 3,3; 0,0 ± 0. vs. 5,0 ± 3,0; 0,4 ± 0,9 vs. 4,0 ± 2,3, respectively) and lying duration was significantly lower in group B during the first 40 minutes of the experiment (T0 until T35). During this time, group B piglets were lying on the floor for 2,8 ± 2,9 min (vs. 27,3 ± 2,4 min in control piglets), whilst group B piglets seemed restless and kept walking and running around. Group C animals slept most time of the experiment (45,1 ± 2,9 min vs 12,7 ± 2,9 min group C, p $<$ 0,0001).

Excessive vocalization was observed from T20 until T30, where all piglets of group B were vocalizing (score 1,2 ± 05, P = 0,0038) in contrast to piglets of group C (no vocalization of any animal during these periods). A video showing the behaviour observed can be visualized on the following link (https://doi.org/10.17236/sat00309). Piglet number 7 and 8 received butorphanol 25 minutes before this video sequence was taken.

From T25 on until the end of the experiment, 4 of 5 piglets in group B panted moderately to severely and from T35 on severely, whereas none of the control animals exhibited panting. When they were panting severely, all piglets also showed gasping and respiratory distress. Moreover, one animal of group B pressed its head against the walls.

Discussion

This prospective, randomized and blinded experimental study showed that 0,2 mg/kg butorphanol IM induces significant behavioural changes in healthy piglets. In contrast to the animals of the control group, butorphanol-treated piglets were distressed and showed restlessness. They repeatedly seemed to try to escape the fence by jumping up the walls and cried excessively which led to respiratory distress, severe panting and hyperthermia.

The occurrence of excitations caused by butorphanol and other opioids has been reported in other farm animal species[2] as well as in humans,[1] but not in pigs.

In cattle, tremor, propulsive walking and nystagmus were reported,[2] whereas in sheep, severe agitation and distressed behaviour were observed after butorphanol administration.[13] In humans, the effects on mood and behaviour were characterized more precisely: Dizziness, nausea/vomiting, clamminess, sweatiness, headache, vertigo, floating feeling, asthenia, anxiety, euphoria, nervousness, paraesthesia, lethargy, confusion and light headedness are reported.[16] The strange behaviour noted in pigs that had received butorphanol appeared like an undesirable state of panic and suggests that also in this species an alteration in perception and sensation is taking place.

Butorphanol is generally classified as a κ-agonist and partial μ-agonist with a fourfold higher affinity for κ- than for μ-receptors.[16] In humans, the symptoms evoked by butorphanol were attributed predominantly to be mediated at μ-receptors and only to a lesser extent at

κ-opioid receptors (KORs).[17] On the other hand, with butorphanol, even greater impairment of psychomotor performance and more negative subjective effects were recorded than following morphine, a relatively strong μ-agonist.[1] Probands treated with pure κ-agonists reported asthenia and disturbances in perception of space and time. Moreover, weakness, sweatiness, vertigo, difficulty in focusing, dizziness and anxiety occurred.[18]

The observed jumping up the wall in our piglets can be interpreted as a sign of malaise, agitation or panic. Similar excessive locomotor activity was also observed in cattle treated with butorphanol,[2] whereas in horses, forward movement and excitation occurred.[15] In sheep, agitation, frequent distress vocalizations and tachypnoea were described.[14, 19] Frequent vocalizations, severe panting and gasping were also observed in the present study. The vocalizations are most likely a sign of panic or discomfort. The observed panting that got worse over time probably occurred as a result of the concurrently measured increase in body temperature. The exposure to stress in mammals activates the vegetative system and stress hormones are released leading to an increase in body temperature.[20] The administration of opioids probably reinforced this reaction, as it was observed that hyperthermia elicited by stress was reduced in animals lacking dynorphin and absent in enkephalin-knockout-mice. [21] In humans, sweating is a known side effect of butorphanol and κ-agonists,[16, 18, 22] but as pigs are not able to sweat, their only possibility to release heat is via panting. Further it is also known that dyspnea is a key feature of panic.[23]

It is well established that endogenous opioid systems play an important role in stress.[24] KORs mediate the effects of stress[24–26] and KOR activity produces not only analgesia and antinociception, but also psychomimesis, dysphoria and aversion and is pro depressant and anxiogenic.[24, 27]

Another possible mechanism how opioids can induce stress is their inhibitory influence on GABA interneurons, which exerts a tonic control over excitatory amino acid pathways in the midbrain tectum, and thereby controls panic-like reactions.[28, 29] Anatomical studies show that opioid and GABAergic systems are closely linked, and the activity of the same neuron may be regulated directly by both GABA and endogenous opioids.[29, 30]

Conclusions

In the present study, 0,2 mg/kg butorphanol IM in healthy four weeks old piglets induced severe behavioural changes resembling to panic attacks which has not been described in this species before. In other species, similar agitations have been described[2, 13, 16] and it is known that they are commonly not observed when opioids are given to painful or sedated animals. In contrast to other species, the administration of butorphanol in combination with other sedatives and anaesthetics (azaperone, α2-agonists, ketamine) to piglets undergoing castration, caused excitations similar to but less severe than in the present study.[7, 8] As the observed excitations eventually were a consequence of butorphanol administration, it is recommended to search for alternative analgesic plans in piglets undergoing castration.

Declarations

Ethics approval and consent to participate

This study was in accordance with the guidelines for good clinical practice under the bylaws of the Swiss experimental animal research (ZH081/16).

Consent for publication

All authors gave consent to publish the study in the current form.

Availability of data and material

Data are available on request from the authors.

Conflict of interests

There are no competing interests.

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Online-Video

Film 1: The following video shows the behavioural changes caused by butorphanol in piglets. Piglet number 7 and 8 (group B) received butorphanol 25 minutes before this video sequence was taken, while piglets 9 and 10 (group C) received an equal amount of saline 0,9 % intramuscularly.

Authors contributions
VP, RB, PH, DK, RG and DC designed and performed the study. The results were presented by VP and RB. All authors red and approved the final manuscript.

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Le butorphanol induit des comportements anxieux et de la détresse chez les porcelets

Le butorphanol induit des comportements anxieux et de la détresse chez les porcelets Dans une précédente étude utilisant le butorphanol chez les porcs avant la castration réalisée sous anesthésie à l'isoflurane, des effets indésirables sévères ont été rapportés. Cela n'étant pas décrit auparavant chez les porcs, nous avons cherché à étudier les effets du butorphanol chez les porcelets. Dix porcelets âgés de 27 jours ont été répartis aléatoirement (en double aveugle) pour recevoir 0,2 mg/kg de butorphanol (groupe B) ou du sérum physiologique à 0,9% (groupe de contrôle C) par voie intramusculaire. Leur comportement a été évalué pendant 60 minutes par deux observateurs indépendants à partir d'enregistrements vidéo.

Deux à 15 minutes après l'injection, les porcelets du groupe B ont présenté de l'agitation, de la détresse et des vocalisations excessives. L'activité locomotrice a augmenté : lors des 40 premières minutes, les porcelets se sont couchés significativement moins fréquemment ($p=0,034$) et pour des périodes plus courtes ($p=0,0014$) par rapport au groupe C. Les animaux du groupe C ont dormi la majorité du temps de l'expérience ($45,1 \pm 2,9$ minutes dans le groupe C vs $12,7 \pm 2,9$ minutes dans le groupe B, $p<0,0001$). Après avoir reçu du butorphanol, les porcs se sont jetés contre les parois (en moyenne 1,2 fois par minute pendant les 30 premières minutes dans le groupe B vs 0 fois par minute dans le groupe C, $p=0,0011$). Dans le groupe B, un individu a appuyé sa tête contre le mur et quatre ont présenté du halètement. Trente minutes après administration du butorphanol, les porcelets ont développé de l'hyperthermie ($41,0 \pm 0,7$ °C dans le groupe B vs $39,6 \pm 0,3$ °C dans le groupe C, $p=0,0075$).

Les résultats de cette étude révèlent que l'administration de 0,2 mg/kg de butorphanol par voie intramusculaire chez les porcelets induit des effets secondaires importants et similaires à ceux rapportés suite à l'administration d'opioïdes dans d'autres espèces.

Mots-clés: porcelet, anesthésie, butorphanol, effet secondaire, agitation

Il butorfanolo induce un comportamento di ansia e angoscia nei suinetti

In uno studio precedente, l'utilizzo del butorfanolo nei suini prima della castrazione eseguita in anestesia con isoflurano, sono state registrate gravi reazioni avverse. Non essendo queste state riportate in precedenza nei maiali, abbiamo voluto studiare gli effetti del butorfanolo nei suinetti. Dieci suinetti di 27 giorni sono stati suddivisi in modo casuale nel ricevere 0,2 mg/kg di butorfanolo (gruppo B) oppure una soluzione salina 0,9% (gruppo di controllo C) per via intramuscolare. Il loro comportamento è stato valutato per 60 minuti da due osservatori indipendenti tramite l'utilizzo di videoregistrazioni.

Da due a 15 minuti dopo la somministrazione, i suinetti del gruppo B hanno mostrato irrequietezza, angoscia e vocalizzazione eccessiva. L'attività locomotoria è aumentata, i suinetti si sono sdraiati molto meno frequentemente ($p=0,034$) e per periodi più brevi ($p=0,0014$) durante i primi 40 minuti rispetto al gruppo C. Gli animali del gruppo C hanno dormito la maggior parte del tempo dell'esperimento ($45,1 \pm 2,9$ minuti nel gruppo C contro $12,7 \pm 2,9$ minuti nel gruppo B, $p<0,0001$). Dopo aver ricevuto il butorfanolo, i suini hanno cominciato a saltare contro il muro (media 1,2 volte al minuto durante i primi 30 minuti nel gruppo B contro 0 volte al minuto nel gruppo C, $p=0,0011$). Nel gruppo B, un animale ha premuto la testa contro il muro e quattro animali si sono messi ad ansimare e boccheggiare. Trenta minuti dopo la somministrazione di butorfanolo, i suinetti sono diventati ipertermici ($41 \pm 0,7$ °C gruppo B contro $39,6 \pm 0,3$ °C gruppo C, $p=0,0075$).

I risultati di questo studio mostrano che 0,2 mg/kg di butorfanolo per via intramuscolare induce gravi effetti collaterali nei suinetti senza sofferenza e sono simili a quelli riportati dopo la somministrazione dell'oppioide in altre specie.

Parole chiave: suinetto, anestesia, butorfanolo, effetti collaterali, irrequietezza

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