Adverse Reactions to Fentanyl Transdermal Patches in Juvenile Calves

A.S. Leaflet R3318

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Summary and Implications

Fentanyl is an extremely potent pain relieving drug that has multiple applications in research and veterinary medicine. Available in a patch, for some species this presents a convenient way to provide long-term pain relief from a surgical or research procedure. This report describes the adverse reactions, clinical outcomes, and treatment for fentanyl patches when applied to healthy and hospitalized calves. Researchers and practitioners should be cautions when utilizing these patches on calves, and utilize doses below 1 ug/kg/kr.

Introduction

Fentanyl is a mu-opioid agonist with approximately 100 times the pain-relieving potency of morphine, that has a short duration of action when administered as a single intravenous bolus. For long-term analgesia, a Fentanyl Transdermal Patch (FTP) has been developed for humans, and has been successfully reported for use in small animals, sheep, goats, horses, and pigs.

Adverse effects described in large animal species include sedation in sheep; vocalization (bleating), and excitement in goats; as well as increased locomotor responses in horses. There are no studies reporting any adverse effects of FTP in cattle, and only one letter to the editor describing a case of a patch being used in a calf.

The purpose of this study was to report any adverse effects from the placement of FTP on calves, and to generate concentration vs. time data for FTP use in calves. While the cost of FTP could potentially exclude their use as an analgesic method for adult cattle, the patches are ideally sized for calves. The hypothesis of this study was that any observed effects would be mild and consistent with those seen in other large animal species.

Materials and Methods

This study was approved by the Animal Care and Use Committee of Iowa State University (protocols 6-16-8301 and 7-16-8318), and consisted of six female Holstein calves and one male Angus calf.

Two studies were initiated. One utilizing prospective healthy calves from the university dairy, and the second a clinical trial for privately owned animals presented to the Food Animal and Camelid Hospital (FACH). After the first adverse effects were reported, the dose was decreased to half what was described for sheep (from 2 ug/kg/hr to 1 ug/kg/hr). After adverse effects were noted at this reduced dose the study was terminated for animal safety concerns. Calves were classified based on the degree of adverse effects noted: no adverse effects (NA), mild adverse effects (MA), and severe adverse effects (SA).

The Holstein calves were between 3 and 4 weeks of age (52.9 +/- 5.2 kg) and the Angus calf was 16 weeks old (171.0 kg). All calves were individually housed in a climate-controlled facility. An intravenous catheter was placed in the jugular vein for blood sample collection.

FTP dosing was initially a dose of 2 ug/kg/hr, then after reaction were observed it was reduced to 1 ug/kg/hr and rounded to the nearest whole patch size. Patches were placed on the antebrachial region as described for sheep[2], and calves were monitored at minimum of every other hour. In the event that an adverse effect was noted and deemed deleterious to animal health by the attending veterinarian, the patch was removed. Planned sampling timepoints were 0, 2, 4, 6, 12, 24, 36, 48, 60, 72, 84, and 96 hours post application, with patch removal at 72 hours after application.

At each sampling timepoint blood was collected from the catheter using a syringe and placed into sodium heparin tubes. The samples were then centrifuged at 1500 G for 10 minutes. The plasma was then stored at -80 C until analysis.

Plasma concentrations of fentanyl, and two of its metabolites, norfentanyl and despropionyl fentanyl, were determined by liquid chromatography-mass spectrometry (LC-MS) after precipitation of proteins by acetonitrile. The limit of quantification for fentanyl and its metabolites via this assay was 0.03 ng/mL.

Results and Discussion

No fentanyl metabolites were observed via the assay. Fentanyl time versus concentration information is displayed in Figure 1.

Two calves (NA) had FTP applied for the entire 72 hour period, with no adverse effects. Two calves had severe reactions (SA) to the FTP. These calves demonstrated hyperthermia, tachycardia, tachypnea, excessive vocalization, excitement and ultimately recumbency before the FTP were removed and Naloxone was administered. Three calves had moderate reactions (MA), and they had their FTP removed.

Both SA and MA groups returned to normal vital parameters within 2-4 hours of FTP removal. The adverse effects noted and physical exam findings for the calves are

displayed in Table 1. No long-term health consequences due to FTP was observed in any group.

Conclusions

FTP applied to calves can achieve serum levels consistent with analgesia in other species (example: > 0.95 ug/mL in dogs). However, there appears to be a population, dose, or conditions that can present adverse effects when FTP is presented to calves. In horses a polymorphism has been associated with an increased locomotor response when fentanyl is administered to horses with the polymorphism[6]. It is unknown at this time if cattle possess such a polymorphism.

Preliminary pharmacokinetic data suggests that parameters are higher in calves when compared to sheep administered the same dose. Future studies should evaluate the effects of lower dosages of FTP on calves. It is noteworthy that no metabolites of fentanyl were detected by the assay, as when fentanyl is administered to calves intravenously norfentanyl is detectable.

This study was limited by a small samples size of animals, as well as differing variables between groups with respect to physiologic status (pain, disease) as well as other drug administration.

Clinicians who utilize an FTP for analgesia in calves should monitor closely for hyperthermia, tachycardia, tachypnea, vocalization, excitement, and recumbency. If noted, patches should be removed and naloxone may be administered. Clinicians should use FTPs judiciously and consider doses at or below 1 ug/kg/kr.

Table 1: Adverse effects noted in study calves.

Calf	Temperature F (maximum)	Heart rate (beats/min)	Respiratory Rate (breaths/min)	Excessive Vocalization	Excitement	Recumbent
NA 1	101.8 F	116	36	-	-	-
NA 2	102.5 F	120	30	-	-	-
SA 1	**104.9 F**	**210**	**72**	+	+	+
SA 2	**105.1 F**	**180**	**78**	+	+	+
MA 1	102.4 F	**174**	**66**	-	-	-
MA 2	**103.5 F**	**180**	**72**	+	+	-
MA 3	**103.7 F**	**196**	**72**	+	+	-
Normal Range	101.5- 103 F	100-140	30-60	n/a	n/a	n/a

Note: NA: Non affected calves, dosed at 2 ug/kg/hr
SA: Severely affected calves, dosed at 2 ug/kg/hr
MA: Moderately affected calves, dosed at 1 ug/kg/hr
Bold: Indicates elevation from normal values
All values for SA and MA calves taken immediately prior to patch removal

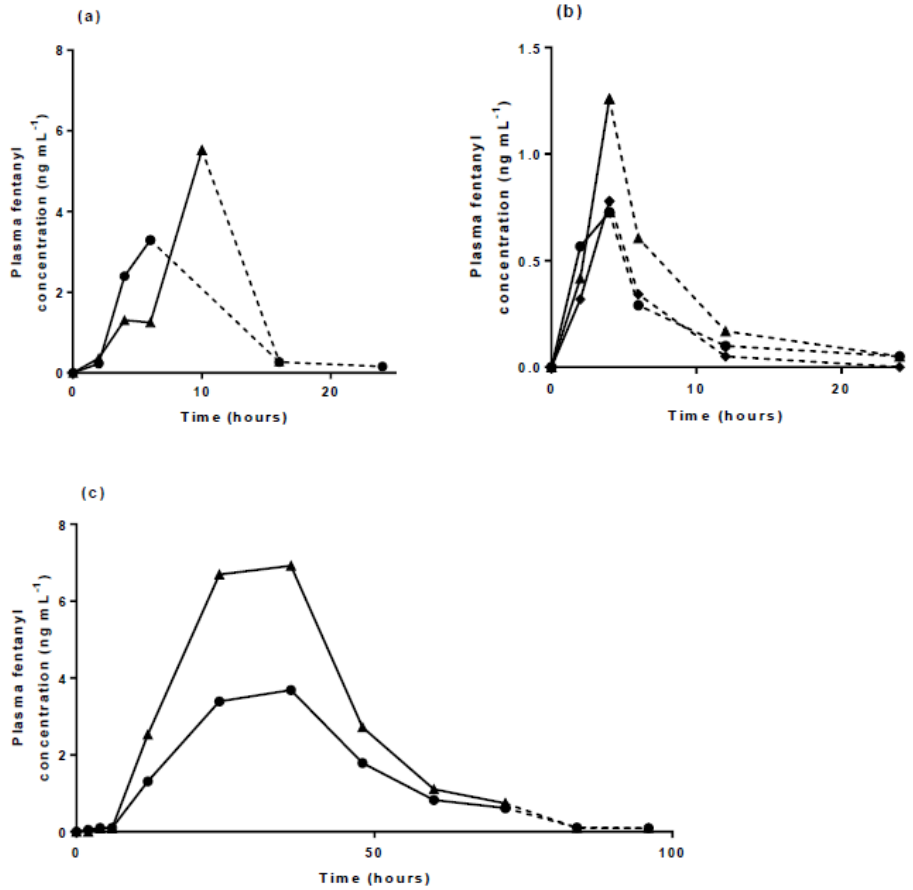

Figure 1: Individual fentanyl time versus concentration data for the study calves

Note:

(a): Severely affected calves, dosed at 2 ug/kg/hr

(b): Moderately affected calves, dosed at 1 ug/kg/hr

(c): Non affected calves, dosed at 2 ug/kg/hr

Dashed line: corresponds to period of time where FTP was removed