ADMINISTRATION OF PHARMACEUTICALS AND VACCINES VIA REMOTE DELIVERY IN BIODEGRADABLE, NEEDLE-LESS IMPLANTS

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SUMMARY

Five experiments were conducted to characterize animal and tissue responses to needle-less implant administration. In Experiment 1, 3 heifers were administered needle-less implants 12, 24, and 36 hours before euthanasia. Slits in the skin smaller than the diameter of the implants, subcutaneous hemorrhaging, and penetration tracts in the muscle were observed at necropsy. However, no portion of the skin, foreign material, or intact portions of the needle-less implants were detected in the musculature at any time after administration. In Experiment 2, 514 beef cows, beef heifers, and dairy heifers administered needle-less implants in the front leg musculature had scab formation or swelling .84 ± .06 cm in diameter two days after treatment but swelling was gone 30 days after treatment. In Experiment 3, only one of five heifers treated with needle-less implants 32 days earlier had a discernable tissue blemish-a .2 x 1.0 cm scar containing connective and adipose tissues. In Experiment 4, 6 white-tailed deer were remotely delivered needle-less implants from concealed positions. Twenty minutes later they and eight control deer were killed instantly using a high-powered rifle shot to the head. Cardiac blood cortisol concentrations (4.0 ± .5 and 5.0 ± .9 ng/mL for control and treated deer, respectively) were similar ($P > .25$). In Experiment 5, four cannulated heifers were administered needle-less implants or injections of saline in a replicated Latin-square design. After treatment, blood cortisol concentrations increased similarly ($P > .25$) to mean maximum concentrations of 9.1 and 10.2 ng/mL (needle-less implant and injected heifers, respectively) 10 to 20 minutes after treatment. In summary, needle-less implants effectively penetrated tissues with minimal stress caused upon the treated animals and dissolved quickly within the tissues.

INTRODUCTION

Administration of pharmaceuticals and vaccines using traditional methods is laborious and requires animal restraint to be accomplished. There is risk of injury, stress compromises recovery rates, and normal physiological processes can be altered. Researchers have demonstrated that stress associated with transport or venipuncture affects the preovulatory luteinizing hormone (LH) surge (Nanda et al., 1989) and suppresses fertility (Hixon et al., 1981; Kesler and Favero, 1996) in cattle. Also, glucocorticoids, which are released upon processing and injecting animals, compromise the recovery of cattle with bovine respiratory disease to antimicrobial therapy (Christie et al., 1977).

A new delivery system utilizing needle-less implants has been developed that allows remote delivery of substances via implantation. The purpose of this paper is to describe the delivery system, characterize tissue penetration and response, and quantify the stress levels of animals administered needle-less implants. Other needle-less implant delivery systems, including the BallistiVet system, have been developed but differ from the system described in this article. Results presented in this article are only relevant for this delivery system and not others. Furthermore, results of other delivery systems are not necessary relevant to the system described herein.

MATERIALS AND METHODS

Delivery System. A remote delivery system used operates on the basis of compressed air (DeNicola et al., 1996a). The delivery system included an adjustable regulator and tank containing compressed air. For all experiments conducted herein, needle-less implants were administered at a distance of 3-6 m from the animals.

Needle-less Implants. The needle-less implants were delivered remotely (Kesler and Favero, 1989; Willis et al., 1994; Jacobsen et al., 1995; DeNicola et al., 1996a; DeNicola et al., 1996b; Kesler, 1996; DeNicola et al., 1997a; DeNicola et al., 1997b; Kesler and Favero, 1997) and were manufactured from two major components. First, they were composed of the outer shell which was manufactured from food grade biodegradable and biocompatable food additives (U.S. Government, 1993). The outer biodegradable shell was 0.635 cm in diameter and 2.0 cm long. The second component consists of the active material (along with some tableting lubricant and controlled release excipients) in the form of a compressed tablet (Kesler, 1993) and was approximately 0.40 cm in diameter and 1.4 cm long. No active material was included in needle-less implants used in these experiments.

Experiment 1

Three beef calves were administered three needle-less implants each into the lower rear leg musculature with a pressure setting of 1,100 to 1,300 psi. Implants were administered at 12 hour intervals for two days in a row. Twelve hours after the last implantation, the calves were euthanized via the captive-bolt method. After euthanasia, the skin was manually pulled from the carcass in a posterior to anterior manner. Administration sites were observed and reactions, noted by discoloration and/or texture of the tissue, that remained on the carcasses were recorded. The tissues underneath the implant penetration sites were dissected in order to identify the final position of the implant. Upon identification of the final position of the implant, gross observations were made of the surrounding tissue.

Experiment 2

Five hundred and fourteen beef cows, beef heifers, and dairy heifers from six locations (location 1 [Western Illinois]-40 beef cows, location 2 [Texas]-39 beef heifers, location 3 [Florida]-43 dairy heifers, location 4 [Wisconsin]-61 dairy heifers, location 5 [Southern Illinois]-291 beef heifers, and location 6 [Eastern Illinois]-40 dairy heifers) were included in this experiment. Females were all administered needle-less implants in the front leg musculature with a pressure setting of 1,100 to 1,300 psi while restrained in a chute and observed for needle-less implant penetration. Administration sites were examined 2 and 30 days after treatment for tissue response to implant administration.

Experiment 3

Needle-less implants were administered to five beef heifers in the right front leg musculature. Thirty-two days after administration, heifers were slaughtered at the University of Illinois Meat Science abattoir. After the carcasses were chilled, the right foreshank musculature of each heifer was dissected and examined for administration site blemishes or other tissue damage.

Experiment 4

Administration of needle-less implants was evaluated on a confined deer herd in southern Connecticut. Deer were habituated to the presence of humans, and all deer were identified with individually numbered ear tags. The facility was 1.76 km^2 of predominantly wooded habitat. Each of six deer, which previously had been selected for removal, were treated with needle-less implants in one of the animal's hindquarters at a pressure setting ranging from 520 to 650 psi (DeNicola et al., 1996a). Approximately 20 minutes later, each deer was killed instantly using a high-powered rifle shot to the head. Within 5 minutes of being shot blood was collected from each of the animals via cardiac puncture. In all cases the rifle shots and the needle-less implants were delivered from concealed positions. Behavioral reactions by the deer before and after being treated with a needle-less implant were noted and recorded. Another group of eight deer, also previously identified for removal, was each killed instantly using a high-powered rifle shot to the head without being administered a needle-less implant. Within 5 minutes, a blood sample was collected from each of the animals via cardiac puncture. Sera was harvested from the blood samples after centrifugation at 1,660 x g for 15 minutes. Sera samples were stored at -20^{o}C until they were assayed for cortisol concentrations. In all cases the rifle shots were fired from concealed positions.

Experiment 5

Four heifers were included in a replicated 2 x 2 Latin-square design. Heifers were intramuscularly administered either an injection of 5 mL of sterile saline via a 5-cc syringe and a 18-g needle that was 3.81 cm long or needle-less implants using a pressure setting of 1,100 to 1,300 psi. Blood samples were collected from catheters fitted 12 to 18 hours before treatments were administered (Aldrich et al., 1996). Collections were made 10 minutes before treatment, and 10, 20, 40, 60, and 80 minutes after treatments. For blood collection the heifers were held in a chute. Serum was harvested from the blood samples after centrifugation at 1,660 x g for 15 minutes and sera were stored at -20^{o}C until assaying it for cortisol concentrations.

Cortisol Assay. Cortisol was extracted by vigorously mixing on a mechanical shaker 100 µL of sera with one mL of diethyl ether in 12 X 75 mm glass culture tubes for 30 seconds. The diethyl ether was decanted into 12 X 75 mm glass culture tubes after freezing the mixture at -20^{o}C. After evaporation of the ether (by heating the tubes in a 60^{o}C water bath), the cortisol was reconstituted into 1 mL of a potassium phosphate buffer by vigorously mixing on a mechanical shaker the contents of the tubes for 30 seconds (.1 µL serum/1 µL buffer). Cortisol concentrations were determined using commercially available cortisol enzyme linked immunoabsorbent assay (ELISA) kits. Seven standards (0, 2, 4, 10, 20, 40, and 100 ng/mL) were included in the assay. Standards (50 µL) or samples (50 µL) and cortisol-peroxidase conjugate (50 µL) were added to the micotiter plates (which were coated with anti-cortisol monoclonal antibody) for one hour at room temperature. Assay components were then discarded and washed from the plates and 150 µL of substrate was added for 30 minutes. Absorbance was then determined at 630 nm and samples were quantified using logit/log transformation. Cortisol concentrations were reported as ng/mL by correcting (correction factor = 200) for volume assayed. Assay of cortisol concentrations was completed within six hours of beginning the extraction.

The assay had 3.4%, 2.1%, and 2.0% crossreactivity with corticosterone, cortisone, and deoxycorticosterone, respectively, and less than 1.0% crossreactivity with 17-hydroxyprogesterone, androstenedione, progesterone, testosterone, aldosterone, dehydroepiandrosterone, estrone, estradiol,

and pregnenolone. Serum samples (n = 4; one mL each) containing 2.27 ng/mL of cortisol spiked with 20 ng of cortisol were determined to have 21.14 ng/mL demonstrating that the extraction procedure was approximately 94.6% efficient. In addition, two heifers that were stressed by normal handling, as defined by methodology of Tulloh (1961), were bled and cortisol concentrations determined along with the experimental samples. Mean serum cortisol concentrations in these heifers were determined to be 36.8 ng/mL. All samples were assayed in one assay and the intraassay coefficient of variation was 4.6%.

Blood cortisol concentrations in Experiment 3 were analyzed by analysis of variance (Hicks, 1964) and in Experiment 4 by split plot analysis of variance (Gill and Hafs, 1971).

RESULTS AND DISCUSSION

The delivery system propels the needle-less implants on the basis of compressed air. The needle-less implant has an internal cavity, open on one end of the shell, capable of holding approximately 275 mg of active compound and controlled release excipients. The other end of the outer shell is pointed and serves as the end that has initial contact with the animal's tissues during penetration. It has been demonstrated that upon contact with the skin, the needle-less implant first causes the skin to stretch (Gould, 1984). The implant penetrates the skin by producing a slit which contracts back to its original form leaving behind a slit shorter than the diameter of the implant (Experiment 1). All 528 needle-less implants penetrated beyond the skin in Experiments 1, 2, and 3. Minimal bleeding, as only a few or several drops of blood were apparent after treatment in Experiment 2, occurred after penetration and that was followed by scab formation (Experiment 2).

Upon entry into living tissue the outer shell dissolved in approximately six hours (Kesler, 1996). A raised welt developed on the skin at the point of implant entry after administration (Experiments 1 and 2). A focal area of hemorrhage was present subcutaneous to the penetration slit (Experiment 1). The muscle had a slit in association with this hemorrhage and the penetration tracts had small darkened areas due to damage of myofibrils. The needle-less implants penetrated the muscle 3 to 8 cm. Although the penetration tracts had small darkened areas, no portion of the skin, foreign material, or intact portions of the needle-less implants were found within the musculature (Experiment 1). In deer, necropsies conducted within one hour of implant administration similarly revealed little tissue damage and minimal intramuscular hemorrhaging and the implant shell was almost completely dissolved (DeNicola et al., 1996a; Swartz et al., 1997). Only a soft gelatinous appearing substance remained in the musculature. Cattle in Experiment 2 had scab formation or swelling .84 ± .06 cm in diameter 2 days after treatment that was gone 30 days after treatment. In Experiment 3, only one of five heifers administered needle-less implants 32 days earlier had a detectable blemish to the muscle-a .2 x 1.0 cm scar containing connective and adipose tissues. One year post-treatment, musculature appeared normal and no lesions, scarring, or implant shell materials were noted in deer (DeNicola et al., 1996a).

The needle-less implant has been propelled from differing compressed air delivery systems. Compressed air used to propel the implant can be generated via a piston (within the delivery system) or obtained from an external tank. Regardless of the source of compressed air, a specific pressure setting is required depending on the species being treated (DeNicola et al., 1996a). A pressure setting of 520 to 650 psi was used in Experiment 4 because DeNicola et al. (1996a) determined that

it was a more appropriate pressure setting for deer. The 1,100 to 1,300 psi pressure setting was necessary for delivery of needle-less implants into mature cattle (Experiments 1, 2, 3, and 5) which have a much thicker skin than deer (Kesler, 1996).

In Experiment 4, serum cortisol concentrations for the deer administered the needle-less implant (5.0 ± .9 ng/mL) were similar ($P > .25$) to cortisol concentrations (4.0 ± .5 ng/mL) in control deer (Table 1). After being treated with a needle-less implant, deer typically flinched or jumped, then walked away seemingly curious about what had occurred. One deer favored the treated leg after treatment but only for a few steps. Similar results were reported by Swartz et al. (1997). Although more adverse reactions were noted when Jacobsen et al. (1995) administered contraceptive needle-less implants to black-tailed deer, the needle-less implants were delivered with a higher pressure setting of 1,100 to 1,300 psi in that study.

One or more of three behavioral reactions were displayed by the cattle upon treatment. The cattle kicked, turned their head to observe the site, or displayed no reaction. In cattle (Experiment 5), the elevation in blood cortisol concentrations subsequent to needle-less implant administration was similar ($P > .25$) to the elevation in blood cortisol concentrations subsequent to an injection (Figure 1). Cortisol concentrations were lower than concentrations (52 ± 32 ng/mL) reported for calves weaned and transported (Faulkner et al., 1992; Table 1). They were similar to cortisol concentrations subsequent to injection (Alam and Dobson, 1986), rectal palpation of the reproductive tract (Alam and Dobson, 1986), and venipuncture (Alam and Dobson, 1986) by other researchers. Other than species, a difference between Experiments 4 and 5 is that although the heifers in Experiment 5 were cannulated, they were handled and restrained for administration of the injection and the needle-less implant. In Experiment 4, the deer were administered the needle-less implant from concealed positions. Therefore, the small elevation in blood cortisol concentrations observed in the heifers may have been due to handling and restraint.

There are several attributes, as described in Table 2, that may be considered regarding the acceptability of a delivery system. The remote needle-less delivery system described herein satisfies several (numbers 1, 2, 3, 4, 5, 6, 8, and 9) of these criteria. More discussion on attribute seven and 10 follow.

This study was not designed to thoroughly investigate the effect of the needle-less implant on tissue damage and lesions (attribute seven; Table 2). Although less of a concern in wild animals, alterations of the musculature due to treatments are important in food animals. Several publications have reported tissue damage after intramuscular injection of various compounds (Dexter et al., 1994; Stokka et al., 1994; George et al., 1995a; George et al., 1995b; George et al., 1996; Rogers et al., 1996). Although clostridial vaccines and long-acting oxytetracycline antibiotics appear to cause a higher incidence of injection site lesions, Rasmussen and Svendsen (1976) and George et al. (1996) demonstrated that saline or excipients alone caused damage to porcine tissue suggesting that the injection site lesions observed may be due to more than just the pharmaceuticals or vaccines being administered. The tissue damage due to intramuscular injection was more extensive than observed in the five heifers included in Experiment 3 (Dexter et al., 1994; Stokka et al., 1994; George et al., 1995a; George et al., 1995b; George et al., 1996; Rogers et al., 1996). The neck and front leg musculature may be the most appropriate administration sites as these muscles are lower quality cuts of meat. Although the needle-less implants were administered intramuscularly in these experiments,

a novel needle-less implant design has been developed and tested that permits remote delivery with subcutaneous implantation (Swartz et al., 1997).

Minimizing repeat therapy (attribute 10; Table 2) depends on the controlled release of product from the needle-less implant. Researchers have discovered several desirable delivery profiles via formulating novel modifications of the needle-less implant (Table 3). Some products, tranquilizers for example, must be immediately available upon entry within the tissues. A needle-less implant design has been developed and tested that effects recumbency in 64 ± 6 seconds; a similar interval to recumbency when remote syringe darts were used (46 ± 12 seconds) (Swartz et al., 1997). An efficacious needle-less implant design has been developed and tested for a compound (prostaglandin $F_{2\alpha}$; $PGF_{2\alpha}$) that has a half-life of less than one minute (Kesler and Favero, 1989; DeNicola et al., 1997b; Table 3). In another situation, a sustained release needle-less implant was developed and demonstrated to prevent reproduction in wild deer for one year (Jacobsen et al., 1995; DeNicola, et al., 1997a; Kesler, 1996). A sustained release needle-less implant was developed in which one 250-mg cephalosporin implant was demonstrated to be as effective in treating bovine respiratory disease as three daily 250 mg injections (Kesler and Bechtol, 1998).

There are many situations where it may be appropriate to administer pharmaceuticals and vaccines via a needle-less implant. The most obvious is in wild animals that are difficult or impossible to restrain. Other situations involve cases where the stress induced by restraint may either impede normal physiology or compromise recovery to therapy being administered during the restraint. Remote delivery may also be valuable in improving safety, reducing processing time, reducing stress and the potential for animal injury, et cetera (Table 2). Alternative portals of entry for other methods of delivery include 1) oral or transmucosal, 2) nasal/pulmonary, 3) transdermal without puncture of the skin, and 4) vaginal. However, all of these portals of entry require animal handling for treatment and although they may be less invasive than injection, stress can result because of handling.

IMPLICATIONS

A method of administering pharmaceuticals and vaccines to domestic and wild animals has been developed. Administration of compounds to animals using this system evokes minimal stress and tissue damage. Treatments should be administered in neck and front leg musculature of domestic meat animals in order to insure that they don't have administration-site blemishes in economically important cuts of meat; however, needle-less implant administration-site blemishes were minimal in this study. This delivery system has other advantages over injection delivery and may be used for drugs requiring immediate release and drugs requiring sustained release.

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Table 1. Cortisol concentrations of deer and cattle treated and handled in various ways

Animal	Treatment/Handling	Cortisol Concentrations (ng/mL) Pre-Treatment Control	Post-Treatment Treated	Source
Cattle	Injection[a]	3.9	10.2	Herein
Cattle	Injection[b]	2.1	10.8	Alam and Dobson[h]
Cattle	Palpation[c]	2.1	11.4	Alam and Dobson[h]
Cattle	Venipuncture[d]	2.1	10.8	Alam and Dobson[h]
Cattle	Needle-less Implant	3.9	9.1	Herein
Cattle	Weaning & Transport[e]	---	52.0	Faulkner et al.[i]
Deer	Syringe Dart[f]	---	25.5	Swartz[j]
Deer	Needle-less Implant	4.0	5.0	Herein
Deer	Needle-less Implant	3.1	4.0	Swartz[j]
Deer	Restraint[g]	---	75.9	Wesson et al.[k]

[a]Heifers were intramuscularly administered 5 cc of sterile saline via 18 g needles 3.81 cm long.

[b]Cows were intramuscularly administered 2 cc of sterile saline via 19 g needles 3.81 cm long.

[c]The uterus of luteal phase cows were palpated for 5 minutes.

[d]Cows were tied securely with a rope halter and bled once via jugular venipuncture.

[e]Calves were weaned and then transported to the feedyard at which time they were bled.

[f]Deer were remotely administered a syringe dart containing ketamine HCl and xylazine HCl.

[g]Deer were physically restrained without drug treatment.

[h]Alam and Dobson (1986).

[i]Faulkner et al. (1992).

[j]Swartz et al. (1997).

[k]Wesson et al. (1979).

Table 2. Selected attributes and value of a model delivery system

	Attribute	Value
1.	Simple and convenient to use	Minimize error and labor
2.	Safe for veterinarians/producers	Minimize human injury
3.	Requires minimal processing	Minimize labor
4.	Evokes minimal stress	Reduce the negative effects of stress on performance and recovery to therapy
5.	No treatment induced injury	Improve animal welfare and maximize profits
6.	No chance of mis-dosing	Maximize drug efficacy
7.	No tissue lesions	Improve meat quality and maximize profits
8.	No needles	Avoids broken needles in animal and disposal requirments
9.	Eliminate the transfer of blood products	Reduce the spread of disease
10.	Minimize repeat therapy	Eliminate additional handling and labor

Table 3. Delivery profiles and examples of compounds delivered in needle-less implants

Delivery Profile	Time	Example
Immediate Release	within 1-2 minutes	Succinylcholine Chloride[b]
Rapid Release	within 1-4 hours	Prostaglandin $F_{2\alpha}$[cd] Gonadotropin Releasing Hormone[ce]
Prolonged Delivery	over days or weeks	Luteinizing Hormone[f] Cephalosporin[g]
Pulsed Delivery[a]	over a month	pZP Vaccine[h]
Sustained Delivery	a year or more	Norgestomet[ijk]

[a]Rapid release at the time of treatment and another rapid release about 1 month later.
[b]Swartz et al. (1997)-under authorization and supervision of the University of Georgia's veterinarian and animal care committee.
[c]Kesler and Favero (1989).
[d]DeNicola et al. (1997b).
[e]Kesler and Favero (1997).
[f]DeNicola et al. (1996b).
[g]Kesler et al. (1997).
[h]Willis et al. (1994).
[i]Jacobsen et al. (1995).
[j]DeNicola et al. (1997a).
[k]Kesler (1996).

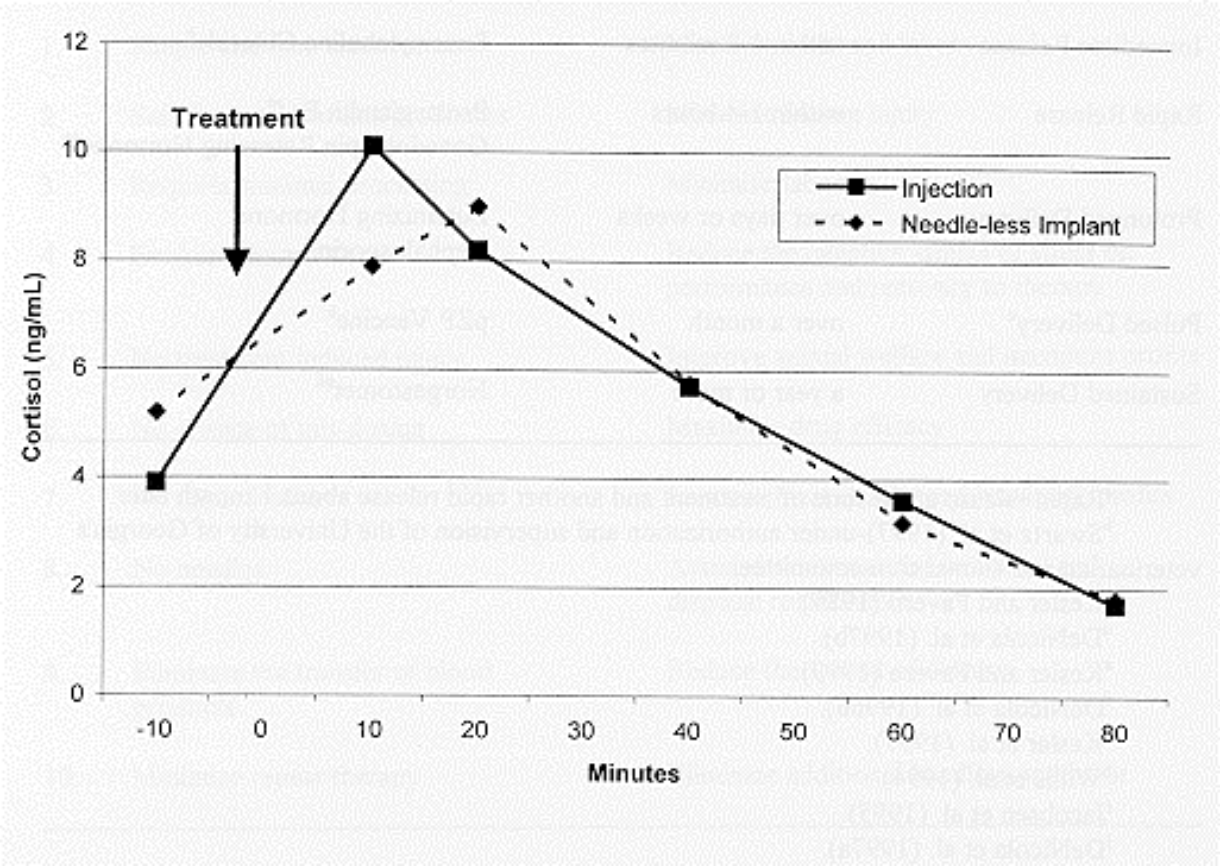

Figure 1. Serum cortisol concentrations (ng/mL) of cannulated heifers before and after administration of needle-less implants or injections.