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INTRADERMAL DELIVERY OF SUBSTANCES

FIELD OF THE INVENTION

The present invention relates to methods for administration of substances into the skin.

BACKGROUND OF THE INVENTION

Conventional needles have long been used to deliver drugs and other substances to humans and animals through the skin, and considerable effort has been made to achieve reproducible and efficacious delivery through the skin while reducing or eliminating the pain associated with conventional needles. Certain transdermal delivery systems eliminate needles entirely, and rely on chemical mediators or external driving forces such as iontophoretic currents or sonophoresis to breach the stratum corneum painlessly and deliver substances through the skin. However, such transdermal delivery systems are not sufficiently reproducible and give variable clinical results.

Mechanical breach of the stratum corneum is still believed to be the most reproducible method of administration of substances through the skin, and it provides the greatest degree of control and reliability. Intramuscular (IM) and subcutaneous (SC) injections are the most commonly used routes of administration. The dermis lies beneath the stratum corneum and epidermis, beginning at a depth of about 60-120 μm below the skin surface in humans, and is approximately 1- 2 mm thick. However, intradermal (ID) injection is rarely used due to the difficulty of correct needle placement in the intradermal space, the difficulty of maintaining placement of the needle in the intradermal space, and a lack of information and knowledge of the pharmacokinetic profiles for many drugs delivered ID. In addition, little is known about fluid absorption limits in dermal tissue and the effect of depot time on drug stability. However, ID administration of drugs and other substances may have several advantages. The intradermal space is close to the capillary bed to allow for absorption and systemic distribution of the substance but is above the peripheral nerve net which may reduce or eliminate injection pain. In addition, there are more suitable and

accessible ID injection sites available for a patient as compared to currently recommended SC administration sites (essentially limited to the abdomen and thigh).

Recent advances in needle design have reduced the pain associated with injections. Smaller gauge and sharper needles reduce tissue damage and therefore decrease the amount of inflammatory mediators released. Of particular interest in this regard are microneedles, which are typically less than 0.2 mm in width and less than 2 mm in length. They are usually fabricated from silicon, plastic or metal and may be hollow for delivery or sampling of substances through a lumen (see, for example, US Patent No. 3,964,482; US Patent No. 5,250,023; US Patent No. 5,876,582; US Patent No. 5,591,139; US Patent No. 5,801,057; US Patent No. 5,928,207; WO 96/17648) or the needles may be solid (see, for example, US Patent No. 5,879,326; WO 96/37256). By selecting an appropriate needle length, the depth of penetration of the microneedle can be controlled to avoid the peripheral nerve net of the skin and reduce or eliminate the sensation of pain. The extremely small diameter of the microneedle and its sharpness also contribute to reduced sensation during the injection. microneedles are known to mechanically porate the stratum corneum and enhance skin permeability (US Patent No. 5,003,987). However, the present inventors have found that, in the case of microneedles, breaching the stratum corneum alone is not sufficient for clinically efficacious intradermal delivery of substances. That is, other factors affect the ability to deliver substances intradermally via small gauge needles in a manner which produces a clinically useful response to the substance.

US Patent No. 5,848,991 describes devices for the controlled delivery of drugs to a limited depth in the skin corresponding to about 0.3-3.0 mm and suggests that such devices are useful for delivery of a variety of drugs, including hormones. US Patent No. 5,957,895 also describes a device for the controlled delivery of drugs wherein the needle may penetrate the skin to a depth of 3 mm or less. The fluid in the pressurized reservoir of the device is gradually discharged under gas pressure through the needle over a predetermined interval, e. g., a solution of insulin delivered over 24 hrs. Neither of these patents indicates that delivery using the devices produces a clinically useful response. Kaushik, et al. have described delivery of insulin into the skin of diabetic rats via microneedles with a detectable reduction in blood glucose levels. These authors do not disclose the depth of penetration of the microneedles nor do they

report any results suggesting a clinically useful glucose response using this method of administration. Further, there is no evidence of accurate or reproducible volume of delivery using such a device. WO 99/64580 suggests that substances may be delivered into skin via microneedles at clinically relevant rates. However, it fails to appreciate that clinical efficacy is dependent upon both accurate, quantitative, and reproducible delivery of a volume or mass of drug substance and the pharmacokinetic uptake and distribution of that substance from the dermal tissue.

SUMMARY OF THE INVENTION

The present invention improves the clinical utility of ID delivery of drugs and other substances to humans or animals. The uses according to the invention involve methods that employ small gauge needles, especially microneedles, placed in the intradermal space to deliver the substance to the intradermal space as a bolus or by infusion. It has been discovered that the placement of the needle outlet within the skin is critical for efficacious delivery of active substances via small gauge needles to prevent leakage of the substance out of the skin and to improve absorption within the intradermal space. ID infusion is a preferred method for delivery according to the invention because lower delivery pressures are required. This also reduces the amount of substance lost to the skin surface due to internal pressure which increases as fluid accumulates within the skin prior to absorption. That is, infusion minimizes effusion of the substance out of the tissue. Infusion also tends to reduce painful swelling and tissue distension and to reduce internal pressure as compared to the corresponding bolus dose. The pharmacokinetics of hormone drugs delivered according to the methods of the uses of the invention have been found to be very similar to the pharmacokinetics of conventional SC delivery of the drug, indicating that ID administration according to the methods of the uses of the invention is likely to produce a similar clinical result (i. e., similar efficacy) with the advantage of reduction or elimination of pain for the patient. Delivery devices which place the needle outlet at an appropriate depth in the intradermal space and control the volume and rate of fluid delivery provide accurate delivery of the substance to the desired location without leakage.

DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates the results of Example 1 for plasma insulin levels during SC and ID infusion of insulin.

Fig. 2 illustrates the results of Example 1 for blood glucose levels during SC and ID infusion of insulin.

Fig. 3 illustrates the results of Example 1 for plasma PTH levels during SC and ID infusion of PTH.

Fig. 4 illustrates the results of Example 2 for plasma insulin levels during SC and ID infusion of insulin at 2 U/hr.

Fig. 5 illustrates the results of Example 2 for plasma glucose levels during SC and ID infusion of insulin at 2 U/hr.

DETAILED DESCRIPTION OF THE INVENTION

In a first aspect of the invention, there is provided use of a substance selected from the group consisting of hormones, antitoxins, substances for the control of pain, substances for the control of thrombosis, substances for the control or elimination of infection and vaccines, for the manufacture of a medicament for use in the treatment or prevention of hormone deficiency, toxicity, pain, thrombosis or infection or in the expression of protective immunity by delivery of said substance into an intradermal space within the skin of a human subject through a small gauge needle inserted into the intradermal space, the needle having an outlet having an exposed height at a depth within the intradermal space sufficient to allow the skin to seal around the needle and the rate and volume of delivery of the substance being controlled, such that leakage of the substance to the surface of skin is substantially prevented. Preferred embodiments of the invention in its first aspect are as described below or as defined in the sub-claims.

The present invention provides delivery of a drug or other substance to a human or animal subject via a device which penetrates the skin to the depth of the intradermal space. The drug or substance is administered into the intradermal space through one or more hollow needles of the device. Substances infused according to the methods of the uses of the invention have been found to exhibit pharmacokinetics similar to that observed for the same substance administered by SC injection, but the ID injection is essentially painless. The methods are particularly applicable to hormone therapy, including insulin and parathyroid hormone (PTH) administration.

The injection device used for ID administration in the uses according to the invention is not critical as long as it penetrates the skin of a subject to a depth sufficient to penetrate the intradermal space without passing through it. In most cases, the device will penetrate the skin to a depth of about 0.5-3 mm, preferably about 1-2 mm. The devices may comprise conventional injection needles, catheters or microneedles of all known types, employed singly or in multiple needle arrays. The terms "needle" and "needles" as used herein are intended to encompass all such needle-like structures. The needles are preferably of small gauge such as microneedles (i. e., smaller than about 25 gauge; typically about 27-35 gauge). The depth of needle penetration may be controlled manually by the practitioner, with or without the assistance of indicator means to indicate when the desired depth is reached. Preferably, however, the device has structural means for limiting skin penetration to the depth of the intradermal space. Such structural means may include limiting the length of the needle or catheter available for penetration so that it is no longer than the depth of the intradermal space. This is most typically accomplished by means of a widened area or "hub" associated with the shaft of the needle, or for needle arrays may take the form of a backing structure or platform to which the needles are attached (see, for example, US Patent 5,879,326; WO 96/37155; WO 96/37256). microneedles are particularly well suited for this purpose, as the length of the microneedle is easily varied during the fabrication process and microneedles are routinely produced in less than 1 mm lengths. microneedles are also very sharp and of very small gauge (typically about 33 gauge or less) to further reduce pain and other sensation during the injection or infusion. They may be used in the invention as individual single-lumen microneedles or multiple microneedles may be assembled or fabricated in linear arrays or two-

dimensional arrays to increase the rate of delivery or the amount of substance delivered in a given period of time. microneedles may be incorporated into a variety of devices such as holders and housings which may also serve to limit the depth of penetration or into catheter sets. the devices of the invention may also incorporate reservoirs to contain the substance prior to delivery or pumps or other means for delivering the drug or other substance under pressure. alternatively, the device housing the microneedles may be linked externally to such additional components.

It has been found that certain features of the intradermal administration protocol are essential for clinically useful pharmacokinetics and dose accuracy. First, it has been found that placement of the needle outlet within the skin significantly affects these parameters. The outlet of a smaller gauge needles with a bevel has a relatively large exposed height (the vertical"rise"of the outlet). Although the needle tip may be placed at the desired depth within the intradermal space, the large exposed height of the needle outlet allows the substance being delivered to be deposited at a much shallower depth nearer the skin surface. As a result, the substance tends to effuse out of the skin due to backpressure exerted by the skin itself and to pressure built up from accumulating fluid from the injection or infusion. For example, 200 μm microneedles are often cited as suitable means for delivery of substances through the skin. We have found, however, that even if the needle outlet is at the tip of such a microneedle (without any bevel) the substance is deposited at too shallow a depth to allow the skin to seal around the needle and the substance readily effuses onto the surface of the skin. Shorter microneedles such as these serve only to permeabilize the skin and do not give sufficient dose control for clinical utility. In contrast, microneedles useful in the invention have a length sufficient to penetrate the intradermal space (the "penetration depth") and an outlet at a depth within the intradermal space (the "outlet depth") which allows the skin to seal around the needle against the backpressure which tends to force the delivered substance toward the skin surface. In general, the needle is no more than about 2 mm long, preferably about 300 μm to 2 mm long, most preferably about 500 μm to 1 mm long. The needle outlet is typically at a depth of about 250 μm to 2 mm when the needle is inserted in the skin, preferably at a depth of about 750 μm to 1.5 mm, and most preferably at a depth of about 1 mm. The exposed height of the needle outlet and the depth of the outlet within the intradermal space influence the extent of sealing by the skin around the needle. That is, at a greater

depth a needle outlet with a greater exposed height will still seal efficiently whereas an outlet with the same exposed height will not seal efficiently when placed at a shallower depth within the intradermal space. Typically, the exposed height of the needle outlet will be from 0 to about 1 mm, preferably from 0 to about 300 μm. A needle outlet with an exposed height of 0 has no bevel and is at the tip of the needle. In this case, the depth of the outlet is the same as the depth of penetration of the needle. A needle outlet which is either formed by a bevel or by an opening through the side of the needle has a measurable exposed height.

Second, it has been found that the pressure of injection or infusion must be carefully controlled due to the high backpressure exerted during ID administration. Gas-pressure driven devices as are known in the prior art are prone to deviations in delivery rate. It is therefore preferable to deliver the substance by placing a constant pressure directly on the liquid interface, as this provides a more constant delivery rate which is essential to optimize absorption and to obtain the desired pharmacokinetics. Delivery rate and volume are also desirably controlled to prevent the formation of weals at the site of delivery and to prevent backpressure from pushing the needle out of the skin. The appropriate delivery rates and volumes to obtain these effects for a selected substance may be determined experimentally using only ordinary skill. That is, in general the size of the weal increases with increasing rate of delivery for infusion and increases with increasing volume for bolus injection. However, the size and number of microneedles and how closely together they are placed can be adjusted to maintain a desired delivery rate or delivery volume without adverse effects on the skin or the stability of the needle in the skin. For example, increasing the spacing between the needles of a microneedle array device or using smaller diameter needles reduces the pressure build-up from unabsorbed fluid in the skin. Such pressure causes weals and pushes the needle out of the skin. Small diameter and increased spacing between multiple needles also allows more rapid absorption at increased rates of delivery or for larger volumes. In addition, we have found that ID infusion or injection often provides higher plasma levels of drug than conventional SC administration, particularly for drugs which are susceptible to in vivo degradation or clearance. This may, in some cases, allow for smaller doses of the substance to be administered through microneedles via the ID route, further reducing concerns about blistering and backpressure.

The administration methods contemplated by the invention include both bolus and infusion delivery of drugs and other substances to human or animal subjects. A bolus dose is a single dose delivered in a single volume unit over a relatively brief time period, typically less than about 5-10 min. Infusion administration comprises administering a fluid at a selected rate (which may be constant or variable) over a relatively more extended time period, typically greater than about 5-10 min. To deliver a substance according to the invention, the needle is placed in the intradermal space and the substance is delivered through the lumen of the needle into the intradermal space where it can act locally or be absorbed by the bloodstream and distributed systemically. The needle may be connected to a reservoir containing the substance to be delivered. Delivery from the reservoir into the intradermal space may occur either passively (without application of external pressure to the substance to be delivered) or actively (with the application of pressure). Examples of preferred pressure-generating means include pumps, syringes, elastomeric membranes, osmotic pressure or Belleville springs or washers. See, for example, US Patent No. 5,957,895; US Patent No. 5,250,023; WO 96/17648; WO 98/11937; WO 99/03521. If desired, the rate of delivery of the substance may be variably controlled by the pressure-generating means. As a result, the substance enters the intradermal space and is absorbed in an amount and at a rate sufficient to produce a clinically efficacious result. by"clinically efficacious result"is meant a clinically useful biological response resulting from administration of a substance. For example, prevention or treatment of a disease or condition is a clinically efficacious result, such as clinically adequate control of blood sugar levels (insulin), clinically adequate management of hormone deficiency (PTH, Growth Hormone), expression of protective immunity (vaccines), or clinically adequate treatment of toxicity (antitoxins). As a further example, a clinically efficacious result also includes control of pain (e. g., using triptans, opioids, analgesics, anesthetics, etc.), thrombosis (e. g., using heparin, coumadin, warfarin, etc.) and control or elimination of infection (e. g., using antibiotics).

EXAMPLE 1

ID infusion of insulin was demonstrated using a stainless steel 30 gauge needle bent at the tip at a 90° angle such that the available length for skin penetration was 1-2 mm.

The needle outlet (the tip of the needle) was at a depth of 1.7-2.0 mm in the skin when the needle was inserted and the total exposed height of the needle outlet was 1.0-1.2 mm. The needle was constructed in a delivery device similar to that described in US Patent No. 5,957,895, with infusion pressure on the insulin reservoir provided by a plastic Belleville spring and gravimetrically measured flow rates of 9 U/hr (90 μL/hr). The corresponding flow rates for SC control infusions were set using MiniMed 507 insulin infusion pumps and Disetronic SC catheter sets. Basal insulin secretion in swine was suppressed by infusion of octreotide acetate (Sandostatinx®, Sandoz Pharmaceuticals, East Hanover, NJ), and hyperglycemia was induced by concommitant infusion of 10% glucose. After a two hour induction and baseline period insulin was infused for 2 hr., followed by a 3 hr. washout period.

Plasma insulin levels were quantitated via a commercial radio-immunoassay (Coat-A-Count® insulin, Diagnostic Products Corporation, Los Angeles, CA), and blood glucose values were measured with a commercial monitor (Accu-chek Advantage®, Boehringer Mannheim Corp, Indianapolis, IN). Weight normalized plasma insulin levels and corresponding blood glucose values are shown in Fig. 1 and Fig. 2. Data indicate similar plasma insulin levels and onset periods for infusion via the ID route and via the conventional SC route. The decrease in blood glucose response is also similar between the two. Although 9 U/hr. is a higher administration rate than is typically used medically, these results also demonstrate the ability of dermal tissues to readily absorb and distribute medicaments which are infused via this pathway.

A similar experiment was conducted using human parathyroid hormone 1-34 (PTH). PTH was infused for a 4 hr. period, followed by a 2 hr. clearance. Flow rates were controlled by a Harvard syringe pump. Control SC infusion was through a standard 31 gauge needle inserted into the SC space lateral to the skin using a "pinch-up" technique. ID infusion was through the bent 30 gauge needle described above. A 0.64 mg/mL PTH solution was infused at a rate of 75 μL/hr. Weight normalized PTH plasma levels are shown in Fig. 3. This data demonstrates the efficacy of this route of administration for additional hormone drugs, and indicates that ID infusion may actually provide higher plasma levels for drugs that are susceptible to *in vivo* biological degradation or clearance.

EXAMPLE 2

ID insulin delivery was demonstrated in swine using a hollow silicon microneedle connected to a standard catheter. The catheter was attached to a MiniMed 507 insulin pump for control of fluid delivery.

A hollow, single-lumen microneedle (2 mm total length and 200 X 100 μm OD, corresponding to about 33 gauge) with an outlet 1.0 μm from the tip (100 μm exposed height) was fabricated using processes known in the art (US Patent No. 5,928,207) and mated to a microbore catheter commonly used for insulin infusion (Disetronic). The distal end of the microneedle was placed into the plastic catheter and cemented in place with epoxy resin to form a depth-limiting hub. The needle outlet was positioned approximately 1 mm beyond the epoxy hub, thus limiting penetration of the needle outlet into the skin to approximately 1 mm., which corresponds to the depth of the intradermal space in swine. The patency of the fluid flow path was confirmed by visual observation, and no obstructions were observed at pressures generated by a standard 1 cc syringe. The catheter was connected to an external insulin infusion pump (MiniMed 507) via the integral Luer connection at the catheter outlet.

The pump was filled with Humalog™ (LisPro) insulin (Lilly) and the catheter and microneedle were primed with insulin according to the manufacturer's instructions. Sandostatin® solution was administered via IV infusion to an anesthetized swine to suppress basal pancreatic function and insulin secretion. After a suitable induction period and baseline sampling, the primed microneedle was inserted perpendicular to the skin surface in the flank of the animal up to the hub stop. Insulin infusion was begun at a rate of 2 U/hr and continued for 4.5 hr. Blood samples were periodically withdrawn and analyzed for serum insulin concentration and blood glucose values using the procedures of Example 1. Baseline insulin levels before infusion were at the background detection level of the assay, as shown in Fig. 4. After initiation of the infusion, serum insulin levels showed an increase which was commensurate with the programmed infusion rates. Blood glucose levels also showed a corresponding drop relative to negative controls (NC) and this drop was similar to the drop observed for conventional SC infusion (Fig. 5).

In this experiment, the microneedle was demonstrated to adequately breach the skin barrier and deliver a drug *in vivo* at pharmaceutical relevant rates. The ID infusion of insulin was demonstrated to be a pharmacokinetically acceptable administration route, and the pharmacodynamic response of blood glucose reduction was also demonstrated. This data indicates a strong probability of successful pharmacological results for ID administration of hormones and other drugs in humans according to the methods of the uses of the invention.

WHAT IS CLAIMED IS:

1. Use of a substance selected from the group consisting of hormones, antitoxins, substances for the control of pain, substances for the control of thrombosis, substances for the control or elimination of infection and vaccines, for the manufacture of a medicament for use in the treatment or prevention of hormone deficiency, toxicity, pain, thrombosis or infection or in the expression of protective immunity by delivery of said substance into an intradermal space within the skin of a human subject through a small gauge needle inserted into the intradermal space, the needle having an outlet giving an exposed height at a depth within the intradermal space sufficient to allow the skin to seal around the needle and the rate and volume of delivery of the substance being controlled, such that leakage of the substance to the surface of skin is substantially prevented.

2. The use of claim 1, wherein the substance is insulin or parathyroid hormone (PTH).

3. The use of claim 1, wherein the substance is an analgesic or an anaesthetic.

4. The use of claim 3, wherein the substance is an opioid or a triptan.

5. The use of claim 1, wherein the substance is heparin, coumadin or warfarin.

6. The use of claim 1, wherein the substance is an antibiotic.

7. The use of claim 1, wherein the needle is smaller than about 25 gauge.

8. The use of claim 1, wherein the needle is selected from the group consisting of microneedles, catheter needles and injection needles.

9. The use of claim 1, wherein a single needle is inserted.

10. The use of claim 1, wherein multiple needles are inserted.

11. The use of claim 1, wherein the substance is a liquid administered by pressure directly on the liquid.

12. The use of claim 1, wherein the substance is infused.

13. The use of claim 1, wherein the substance is injected a bolus.

14. The use of claim 1, wherein the needle is about 300 μm to 2 mm long.

15. The use of claim 14, wherein the needle is about 500 μm to 1 mm long.

16. The use of claim 1, wherein the outlet is at a depth of about 250 μm to 2 mm when the needle is inserted.

17. A use of claim 16, wherein the outlet is at a depth of about 750 μm to 1.5 mm when the needle is inserted.

18. The use of claim 16, wherein the outlet has an exposed height of about 0 to 1 mm.

19. The use of claim 18, wherein the outlet has an exposed height of about 0 to 300 μm.

20. The use of claim 1, wherein delivery rate or volume delivered is controlled by spacing of multiple needles, needle diameter or number of needles.

21. The use of claim 1, wherein the rate and volume of delivery of the substance are controlled so as to prevent the formation of weals at the site of injection and to prevent ejection of the needle.

22. The use of claim 1, wherein a clinically useful amount of the substance ius absorbed systemically from the intradermal space.