A MINIATURE INFUSER FOR THE PULSATILE ADMINISTRATION OF LHRH

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ABSTRACT

This paper describes a compact, battery-powered infuser that is light, unobtrusive and simple to operate. A novel direct-drive method is used to deliver intermittent boluses of hormone at predetermined time intervals via a special prefilled syringe. Normal pregnancy rates were achieved in anovulatory women when infused with luteinising hormone releasing hormone (LHRH).

Keywords: Drug delivery, LHRH, infuser, pulsatile, infertility, ovulation, anovulation, subcutaneous.

INTRODUCTION

Failure of ovulation (anovulation) is an important cause of infertility, and is often a result of decreased pituitary production of the gonadotrophins; follicle stimulating hormone (FSH) and luteinising hormone (LH). While many patients suffering from this condition will respond to anti-oestrogens such as clomiphene citrate, a significant proportion require treatment with human menopausal gonadotrophin (HMG) in order to ovulate. Close biochemical and ultrasonic supervision is essential when using this form of therapy, as it commonly results in multiple conception (20%), and potentially dangerous ovarian hyperstimulation may occur (3%)[1]. These factors therefore preclude its use in patients who are not close to a major infertility centre.

Normal secretion of FSH and LH is dependent upon the pulsatile release of luteinising hormone releasing hormone (LHRH) by the hypothalamus[2]. The availability of synthetic LHRH has made possible the direct stimulation of gonadotrophin release in women with anovulation who do not respond to clomiphene treatment. High-dose injections at infrequent intervals have produced disappointing results, but low-dose infusions that mimic the normal pulsatile secretory behaviour of the hypothalamus are proving extremely effective[3].

Administration of LHRH in this way increases the responsiveness of the pituitary gonadotrophin receptors to further LHRH stimulation[4]. This self-priming effect only occurs when stimulation is in the form of discrete pulses. Pituitary sensitivity falls, and gonadotrophin release decreases when a continuous infusion is given or when the pulse frequency is outside the optimal range[5]. An LHRH pulse interval of between 80 and 116 minutes has been measured in normal women during ovarian follicular maturation. Appropriate growth of the follicle can be demonstrated by serial pelvic ultrasound examinations[6]. This method of gonadotrophin stimulation produces a solitary dominant ovarian follicle, reducing the risk of multiple conception. Following ovulation, the corpus luteum is supported by continuing the pulsatile LHRH infusion.

The authors have developed an automatic infusion system which delivers intermittent boluses of hormone at predetermined pulse intervals. Both bolus volume and time interval are variable, so that the conditions for optimum therapeutic effect may be studied.

DESCRIPTION

Operation

The infuser (*Figure 1*) is a compact, battery-powered syringe driver that is light, unobtrusive and simple to operate. A syringe (A), prefilled with standard strength LHRH is fitted with a plunger (B) and a cannula(C). The cannula is initially primed by hand and the assembly clipped into the infuser with the slider (D) drawn back. The slider is then pushed forward to engage the plunger with the direct drive (E). Further priming can be achieved electrically, but this is considered unnecessary unless the bolus size is less than 60 μl.

Luteinising hormone releasing hormone (LHRH, Hoechst, 100 μg/ml) is delivered in discrete micro-injections (boluses) of a preset size and time
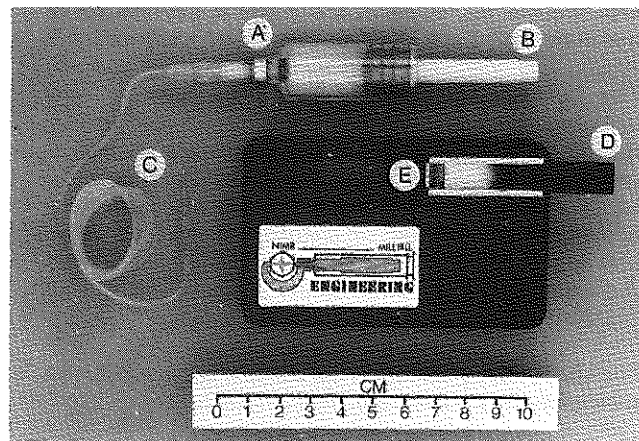

Figure 1 LHRH infuser with syringe and cannula.

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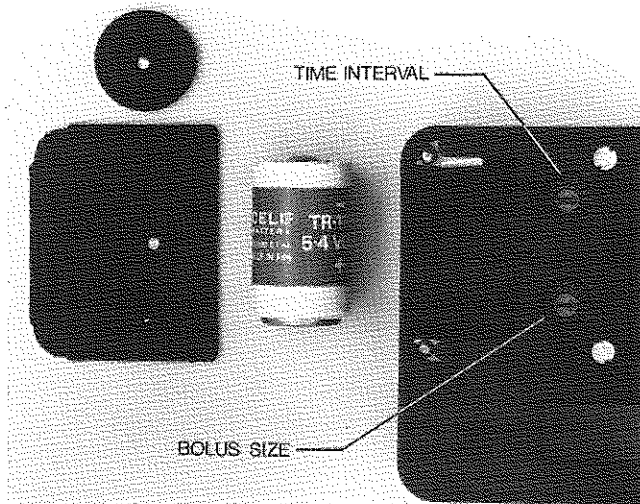
Figure 2 Battery compartment with cover removed showing 16-position time interval and bolus control switches.

Table 1 Pump switch settings.

Switch position	Bolus size (μl)	Time interval (min)
0	20	128
1	40	119
2	60	111
3	80	102
4	100	94
5	120	85
6	140	77
7	160	68
8	180	60
9	200	51
A	220	43
B	240	34
C	260	26
D	280	17
E	300	8.5
F	320	Test position

interval. Following removal of the battery cover, the bolus and time interval control switches (*Figure 2*) are set with a small screwdriver. The range of values available is given in *Table 1*. The test position (F) gives a continuous drive for testing the motor or for priming the cannula. A flashing LED indicates the battery condition.

The infuser is designed to be worn unobtrusively under clothing. It can be worn on the arm, but some patients prefer a waist belt or garter. A site under clothing, close to the body is preferable to maintain the LHRH at an even temperature.

The cannula needle is inserted into the subcutaneous tissue of the arm or the abdominal region. It is important to use a cannula with a dead volume of less than 100 μl to maintain flow accuracy[*]. The patient may take off the pump before active exercise or bathing (it is splashproof but not waterproof), by removing the cannula at the needle end or, alternatively, disconnecting at the syringe, leaving the cannula in place.

For those few patients who do not respond to subcutaneous treatment, intravenous

administration is used. Heparin 500 is added to the LHRH solution (150 IU/ml) and the resulting solution infused via a fine cannula[†] inserted into a forearm vein.

Mechanical design

The mechanism is based on the authors' direct drive insulin infuser[7], redesigned to increase the delivery increment from 0.75 to 5 μl.

The drive principle is similar to a rack and pinion (*Figure 3*). The driving force is transmitted directly to the plain cylindrical plunger (rack) of the syringe via a splined roller (pinion) which forms teeth in the plastic as it turns. The advantages of this drive are its compact size, freedom from backlash and the ease of loading the syringe assembly.

The glass syringe[**] has an effective volume of 5.6 ml. Glass is used in preference to plastic to avoid material contamination of the infused liquid. Both the body and piston are siliconised to minimise static friction.

The plunger is moulded from Kematal[§] which gives excellent dimensional stability and uniform drive characteristics up to plunger loads in excess of 5 kg, equivalent to a syringe pressure of 2 atmospheres in addition to a static load of 1 kg. The plunger and syringe are both disposable.

The gearbox[‡] has four reductions (9:31) to the flag and a further five reductions to the final spline drive shaft. The basic increment of flow is determined by an infra-red photoelectric flag circuit, mounted at an appropriate position in the gearbox. A defined unit of angular rotation is signalled by the flag, and the motor is then stopped. Nylon is used for the first gear to reduce gearbox noise; the remaining gears are hardened steel. Critical tolerances on plunger diameter and spline/slider gap are maintained by good quality control and selective assembly techniques.

The main pump components are the drive unit, the electronics and the case. Assembly is in modular form, the gearbox fitting directly into the
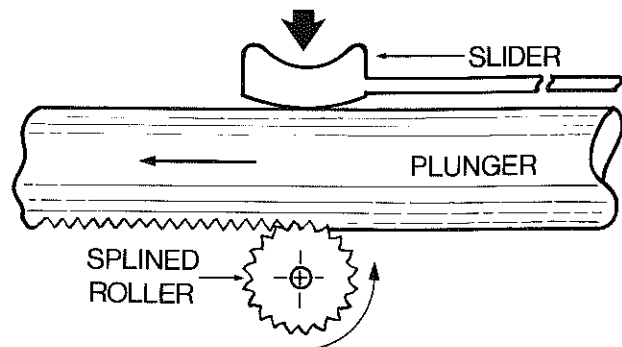

Figure 3 Principle of direct drive.

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case and held in place by the electronics cover. The case, covers and slider are injection moulded in 25% glass reinforced nylon. The two control switches (*Figure 2*) are accessed by removing the battery cover, which is retained by a single thumb-operated screw. Brass-threaded inserts are included in the case mould to ensure secure fitting of the two covers.

Electronic design

While originally conceived as an LHRH infuser, the electronic control has been developed for general-purpose infusion of non-lethal drugs. Complicated alarm and protection circuits are unnecessary, and a simplified design, using standard electronic components, is used, keeping costs and quiescent current to a minimum.

The two 16-position switches control the intermittently delivered bolus volume (as multiples of the basic 5 μl shot volume) and the time interval between boluses. The range of each of the two control variables covered by the switches may be changed by internal circuit reconnection, not accessible to the user.

The circuit is shown schematically in *Figure 4*. A 32.768 kHz oscillator and divider provide a 0.5 Hz clock, which feeds a 14 bit counter. When the counter reaches the same logic state as the binary coded interval switch, the motor starts and is subsequently switched off by the flag signal.

There are two additional timing options; wire links can be hardwired to double or quadruple the time interval range, and a preset time interval can be added to the switch-selected intervals.

The bolus delivery is controlled by a 64 bit shift register which receives optic flags via two Schmitt invertors that shape the signal. Bolus volumes are determined by counting the desired number of 5 μl volume increments. The bolus switch connects to the upper four bits of the six inputs controlling the shift register length. This allows the binary coded switch to set the bolus count from 4 – 64, in increments of 4 (16 steps).

Under normal conditions, an indicator LED shows regular 4s flashes, but these are inhibited if the battery condition is low. If the battery voltage falls below 4.1 V then the ICL8211 short circuits the LED, preventing it from illuminating. The battery is a 5.4 V Mallory TR114N, providing sufficient power for at least 40 days continuous operation.

All circuits are reset following battery insertion, and there is diode protection against battery reversal. The circuit assembly comprises seven standard CMOS circuits arranged with two BCD switches on two piggyback printed circuit boards[*].

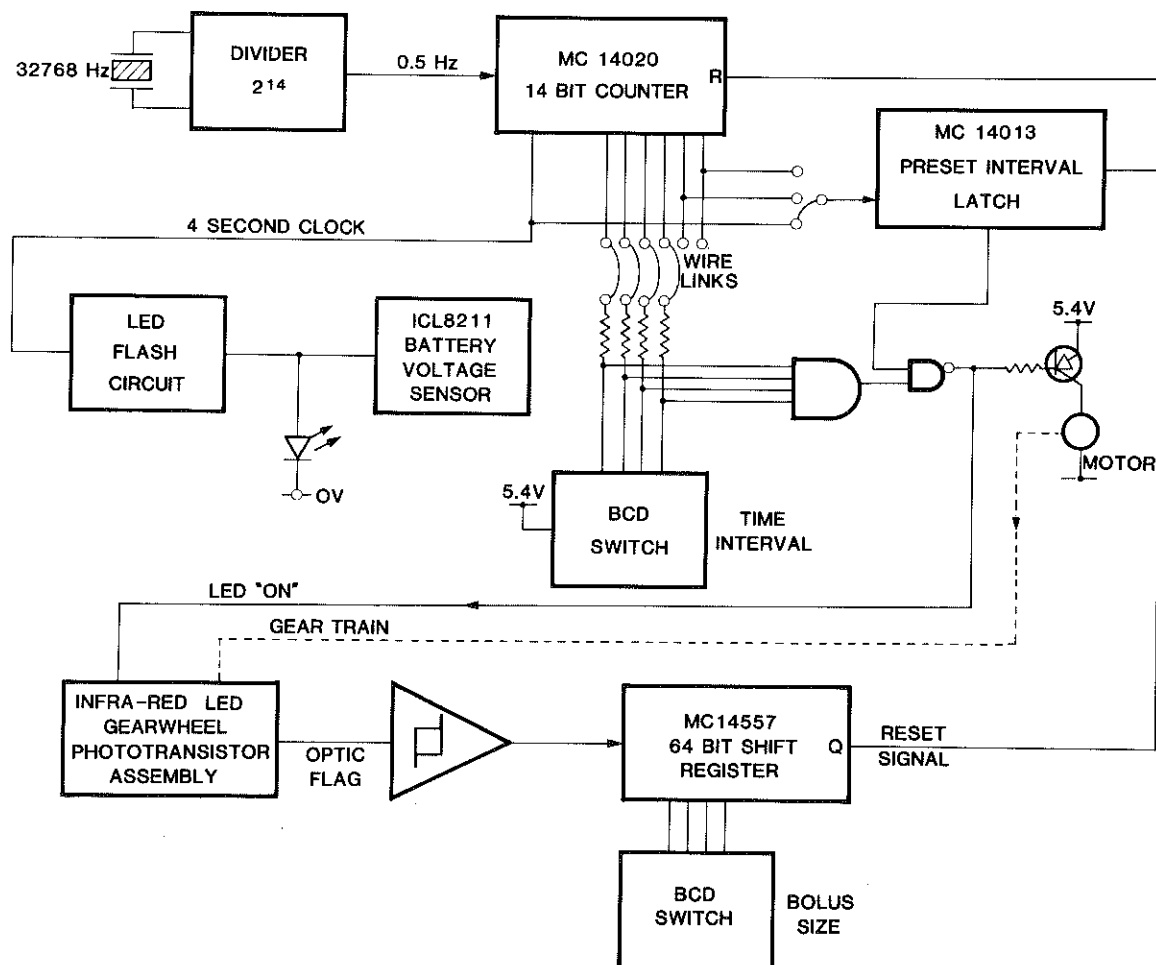---

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Figure 4 Schematic of control circuit.

Table 2 Mean flow measurements for 10 pumps.

Bolus size–time interval (Table 1)	O–E	F–O	2–4	5–5
Design flow (μl/h)	139.0	148.0	38.0	84.0
Measured flow – mean	146.8	155.9	39.1	86.8
Standard deviation	4.3	6.2	1.9	3.5

Table 3 Bolus delivery accuracy for four settings.

Bolus setting (μl)	20.0	100.0	200.0	320.0
Mean bolus volume	21.4	106.9	221.7	354.2
Standard deviation	1.0	1.6	5.2	8.4

Performance testing

Flow tests were performed to evaluate both long- and short-term accuracy.

The mean flow over a 24 h period was measured gravimetrically by collecting the infusate into pre-weighed vials sealed with PTFE septa to prevent evaporation. The results for four different switch combinations on 10 pumps are given in *Table 2*. The mean flows were up to 6% higher than the set values, with a standard deviation of ±4%.

The short-term accuracy was assessed by continuously monitoring the weight of one of the above vials using a precision electronic balance[†] linked to an Apple II computer. The volume of the individual bolus was measured to an accuracy of ±0.1 μl. The bolus delivery accuracy for four ranges is given in *Table 3*. The mean bolus volume was measured to be about 10% higher than the set value, but the bolus-to-bolus volume variation, as measured by the standard deviation, was within ±5%. These results compare very favourably with other infusion pumps using leadscrew and peristaltic drive mechanisms[8].

CLINICAL TRIALS

Using the infusion system described here, 180 ovulatory cycles have been induced in 56 women. Of these, 156 were induced by subcutaneous administration of LHRH. In the remainder, intravenous therapy was used when the patient failed to respond to subcutaneous therapy. In the majority of cycles, the pulse interval was set at 90 min. An increase in the time interval to 120 min after ovulation has occurred seems to have no adverse effect on corpus luteal function. In this group of patients, 39 pregnancies have been confirmed and 10 normal infants have so far been delivered. One multiple pregnancy has occured. The cumulative conception and spontaneous abortion rates appear similar to those reported for the normal population[3].

Patients have usually worn the pump attached to an arm or in a holster around the waist, and have experienced minimal inconvenience. They were encouraged to change the subcutaneous infusion

site every three days. Since the majority of patients needing pulsatile infusions of LHRH respond to subcutaneous therapy, the device can be easily removed for activities such as bathing. Although an erythematous reaction occurred on several occasions at the subcutaneous infusion site, these were never severe enough to necessitate withdrawal of therapy. Thrombophlebitis at the site of the intravenous cannula was diagnosed in three patients; the cannulae were immediately removed and only one patient required systemic antibiotic therapy.

During the equivalent of 15 pump-years of operation there have been one electrical and three mechanical failures. The electrical failure was due to a dry joint on the printed circuit board (PCB) of one of the first prototypes. The mechanical failures were all due to contamination of the optical flag system by the inadvertant use of infra-red opaque grease. There have been no electrical failures following the inclusion of a custom-built PCB, and no mechanical failures since gearboxes have been degreased. Batteries have been found to last approximately 6 weeks before needing replacing.

DISCUSSION

Twenty of the infusion pumps described have been in intensive use at the Middlesex Hospital for over one year. The successful application of pump therapy to the treatment of anovulation with pulsatile LHRH has had two important effects, it has prepared the way for the use of LHRH as a therapeutic agent and it has demonstrated the general suitability of pump therapy for hormone administration.

Although the women reported here were closely monitored during this clinical evaluation, no cases of hyperstimulation were observed. Inherent steroid feedback mechanisms, acting at the level of the pituitary, regulate gonadotrophin synthesis and release. Since the close biochemical supervision required for HMG therapy is therefore unnecessary outpatient management is possible with patients visiting the clinician on perhaps a weekly basis. Syringes pre-filled with LHRH will greatly facilitate this method of treatment.

The accurate delivery of LHRH into the patient is a function of pump accuracy and the absorption characteristics at the injection site. Subcutaneous absorption depends on local blood flow and temperature, and variations can be as high as 30%, depending on the activity of the patient and the choice of injection site. The flow accuracy of the pump is well within this limit. Intravenous absorption, however, is immediate, and so the accuracy of delivery depends essentially on the accuracy of the pump. Of the two pump-flow parameters measured, the bolus-to-bolus volume variation is far more important than the mean flow, particularly when there is a long time interval between boluses. The highest bolus-to-bolus volume variation (±4.7%) occurs with the lowest bolus setting of 20 μl. As errors of up to 10% are tolerable, there is scope for even further reduction in bolus size. The fact that the mean flow was

found to be consistently higher than the set values signifies that the error can be corrected by calibration.

Experience has shown that even smaller pumps and improved cannulation are prime patient requirements. While the current infuser design leaves scope for further reduction in size, particularly thickness, the cannulation problem is not so straightforward. Needle-ended cannulae have to be resited about every three days to avoid excessive irritation, which is mainly caused by the rigidity of the needle. More flexible indwelling cannulae are now available, but these require a large gauge needle to insert them, and they have a high dead volume that can lead to flow inaccuracies. There is clearly a need for a fine-gauge flexible cannula with a non-traumatic method of insertion.

The realisation that other hormones, such as growth hormone and oxytocin, are also released in a pulsatile manner, suggests that chronic intermittent administration using devices similar to that described here may well find considerable clinical application in the near future.

ACKNOWLEDGEMENTS

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LASER METHOD FOR RECORDING DISPLACEMENT OF THE HEART AND CHEST WALL

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ABSTRACT

Several non-invasive methods are in use for recording mechanocardiograms. In this paper a new laser technique will be presented to measure heart motion, chest wall displacement and other displacement curves of cardiovascular structures. Principles of the laser displacement technique are described. The measurement range within which displacement is sensed, is 32 mm with a detector to object distance of 25 cm and a resolution of 8 μm (digital output) or 16 μm (analogue

output). The specific surface of which motion is sensed is 1 mm². The sensitivity of the system is 156 mV/mm at a frequency bandwidth of 0–2 kHz. Assessment of the laser displacement technique was carried out during 6 dog experiments on the closed chest, on the exposed heart, on blood vessels and also on the chest wall of 5 normal subjects. Displacement of the chest wall at the apical site ranges between 0.3–0.8 mm and of the exposed heart between 3–10 mm.

INTRODUCTION

Precordial movements, reflecting the mechanical action of the heart, have been studied since more than 100 years, starting with the pioneer work of Marey and Chauveau.

Its value has been established in the diagnosis and haemodynamic evaluation of various forms of heart disease[1–7]. It has been especially used for the non-invasive timing of left ventricular pressure events[8–12].

Many different methods of recording low-frequency movements are used. In general they fall into two categories: one that records relative motion with reference to the chest wall, usually called apex-cardiography and one that records absolute displacement with reference to an external fixed coordinate system, sometimes called kineto-cardiography[13]. As observations of pulsatile events are not restricted to the cardiac apex, the more general term of mechano-cardiography[14] and sphygmography[15] are also used.

The most commonly used devices for measuring relative motion, include the crystal microphone[16], capacitance pick-up[17], piezo-resistive transducer[18] and fluid filled calibrated pressure measuring system[19]. Absolute motion can be sensed with a bellows mounted on a crossbar[20], or photo-electric devices having no direct contact with the chest-wall[21–22].

The aim of the present study was to evaluate a new technique, using a laser diode beam for recording of absolute motion by means of scattered laser light[23]. The measuring device will be described and results will be given of absolute displacement measurements obtained on the chest wall in dogs

and in humans and of the exposed heart and blood vessels during open thorax experiments.

DESCRIPTION OF THE SYSTEM

The principle of the laser displacement system (LD) (Optocator Selcom, Dimed, Antwerp, Belgium) is shown in *Figure 1*.

A semiconductor laser source (GaAs) emits a pulsed infrared light beam (repetition frequency of each burst of 16 pulses is 16 kHz) at 850 nm. The burst mode of operation avoids interference with other light sources, permits a higher power level for the diode and corresponds with the updating frequency of the detector probe. The laser beam is focused in the centre of the measuring range: peak to peak amplitudes of displacement can range between 0–32 mm. The moving object scatters the beam and acts as a secondary light source. The scattered light is focused on a position sensitive detector (PSD). The position of the object in the measuring range will determine at which place on the PSD the scattered light will be focused, and will give rise to two currents X_1 and X_2.
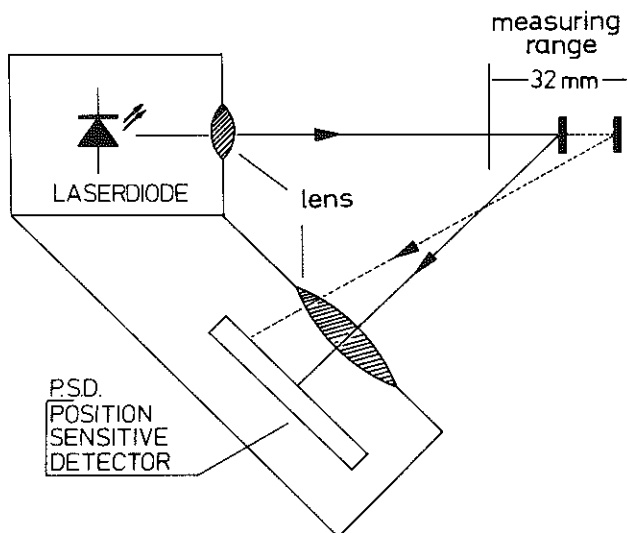

Figure 1   Schematic diagram of laser displacement method.

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