INTELLIGENT INTRA-ORAL THERAPEUTIC DEVICES

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Abstract: The oral cavity is a preferred site for administration of therapy, mainly due to its excellent accessibility. Novel methods are under development, including two international projects funded by the European Union and managed by the authors. The project "Saliwell" is developing an automatic, remotely controlled, electronic saliva-stimulating system supported by a dental implant or appliance, aimed at treating xerostomia. This tooth-sized system restores salivation by neuro-stimulation and comprises of micro-processor, sensor, actuators, batteries, and programmable algorithms for controlling the intensity of stimulation by a remote control. The system's proper functioning and safety is being validated successfully in patients from several European communities. The project "IntelliDrug" is developing a drug delivery micro-system to provide an alternative approach for the treatment of addiction and chronic diseases. The system, which resides in the oral cavity attached to a dental appliance, contains a replaceable medication reservoir and an intelligent medication delivery mechanism, which is fully controlled according to the patient needs. Drugs may be delivered to the oral mucosa and/or the gastro-intestinal tract. *In vivo* studies have demonstrated the feasibility of the delivery concept.

Introduction

The development of electronically based, intra-oral devices has an outstanding potential of using the oral cavity for various medical applications, such as enhancing saliva secretion, controlled drug delivery and medical monitoring. Highly accessible and with unique physiological characteristics, the oral cavity is a suitable interface between the human body and the outer world. The main advantages of the oral cavity are:

- Outstanding accessibility, compared to other mucosal surfaces, such as the nasal, rectal or ocular mucosa
- Minimal cosmetic and discretion concerns (compared to the skin and the rectal mucosa)
- Easy bi-directional transfer of biological substances
- High tolerance to trauma due to multiple defense mechanisms (e.g. the presence of saliva and antimicrobial factors and the rapid epithelial regeneration)
- Rich blood supply, leading to good bioavailability [1]

The present studies have been undertaken to:

1- Evaluate the safety and effectiveness of an electro-stimulator mounted on an individualized intra-oral removable appliance intelligent electro-stimulating device to treat dry mouth.

2- Investigate whether the oral cavity can provide access to efficient and non-invasive drug delivery using an electronic and software driven system in pigs, as part of the development of a remotely controlled, self-contained intra-oral miniature drug delivery device.

Materials and Methods

Salivary electro-stimulator: The electro-stimulator developed by the Saliwell project team is based on applying stimulating signals on the lingual nerve causing the salivary glands to naturally and constantly secrete saliva at an enhanced capacity. Saliwell has developed two basic options: a fixed device named Saliwell Crown (Figures 1 and 2) and a removable device, the Saliwell GenNarino (Figure 3). The implant is placed permanently in the mouth, while the Saliwell Crown is secured by a screw and is renewed and replaced, after batteries ran out of power (a period of about 12 months). Both devices can be applied for one-sided or bilateral stimulation (if the former is not strong enough).

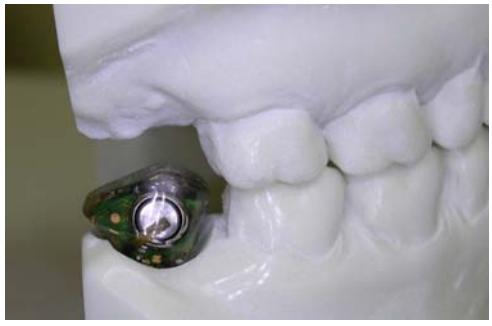

Figure 1: Saliwell Crown is attached to a standard dental implant

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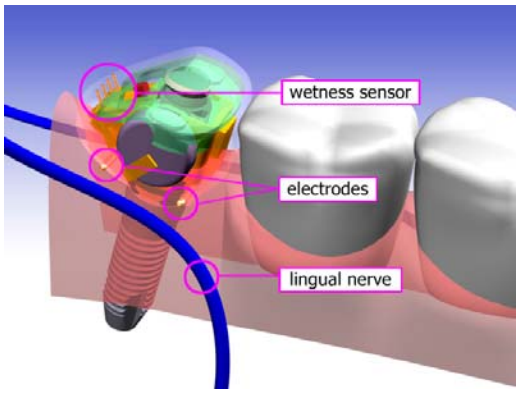

Figure 2: Saliwell Crown is located at the third molar area, close to the lingual nerve, which regulates salivary secretion.

Figure 3: Saliwell GenNarino, where the stimulation electronics are embedded inside a mouth-guard like device and can be taken in and out at the patient's will.

Saliwell devices include a built-in micro-processor with embedded software, an independent power source and stimulation electrodes. Stimulation level is controlled by the patient, based on its subjective momentary needs, using a custom made remote control or automatically by a wetness sensor that provides accurate and totally independent operation.

A first clinical investigation on the Saliwell GenNarino was designed as a cross-over, double-blinded, sham-controlled randomized multi-centre trial. The primary endpoints of the study were defined as a significant decrease of oral dryness as measured by the built-in wetness sensor and an improvement of xerostomia-related symptoms. These parameters obtained during active electro-stimulation were compared to those recorded during sham stimulation by the same device. Experiments were performed in 3 medical centres (Charité Hospital Berlin, Hospital Clínico San Carlos Madrid and Università di Napoli Federico II).

The GenNarino device was produced for each patient individually. A randomized stimulation schedule, with the stimulation pattern for each experiment, was prepared for each patient. These stimulation parameters were included into the software, and were set for each experiment by commands transmitted from the remote control to the GenNarinos. Each experiment consisted of one active stimulation test and one sham test in a random order, both by GenNarino wearing during 10 minutes each, with an interval of 35 minutes between them. Immediately upon GenNarino insertion into patients' mouth, wetness sensor recording started. Finally, patients were asked to subjectively compare the results of both experiments, focusing on dryness changes.

Drug delivery device: The "IntelliDrug" project, also funded by the European Commission, is developing an intraoral micro-system that will be reloaded in a simple non-invasive way (Figure 4).

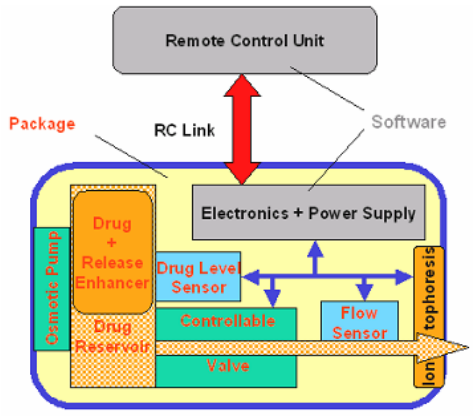

Figure 4: The IntelliDrug system contains a medication replacement reservoir and releases the medication in a controlled, intelligent manner according to the patient needs, in periods lasting days, weeks or months.

The device will allow the control of the administrated quantity of medication, the delivery time and re-balance administration policy, based on real-time sensing and remote control for personal and/or external supervision. Any medication with a need for a controlled release mechanism may be a good candidate for this new type of oral delivery, especially medications with a narrow therapeutic window and/or medication such as pain relief or psychiatric medication that can be optimized by the patient himself using a personal remote control. Naltrexone HCl, an opioid antagonist, is used during the developmental phase.

The IntelliDrug project has built up a drug dosage system for making *in vivo* tests on living pigs. The objectives of these tests are the investigation of the naltrexone blood plasma level achieved by the delivery from the system in relation to intra-venous (i.v.) administration.

The tested drug system has similar components than the final system to be used by humans. The system consists of an extra-oral component (containing a drug reservoir, an actuation mechanism to push the drug solution, a flow sensor, power source and software) and an intra-oral outlet system mounted on a dental prop (Figure 5). The system was tested *in vivo* on 12 pigs in a controlled study over 6 experimental session days. The

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anti-opiate drug naltrexone, in various doses, was delivered by the system to the buccal (cheek) mucosa during 10 minutes or was injected i. v., and its blood levels assessed during 6 hours (Figure 6).

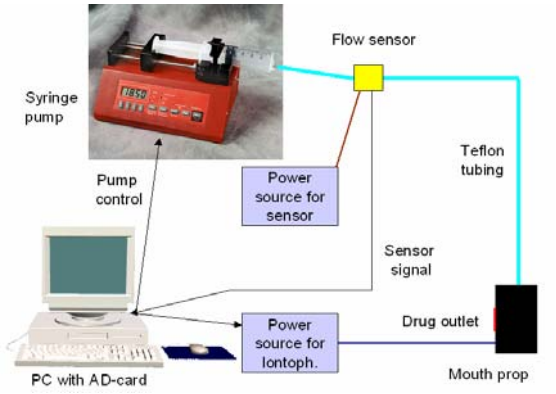

Figure 5: Schematic of the complete system

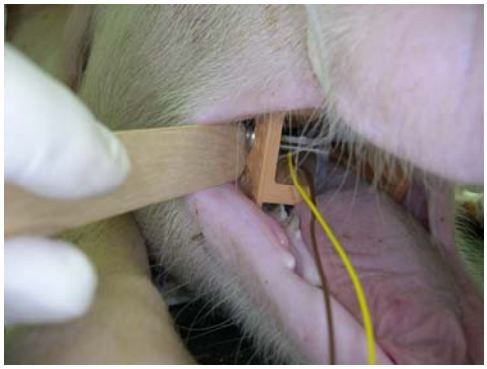

Figure 6: The outlet of the system, and the retrieved cheek, to show its intimate contact with the buccal mucosa

Results

Salivary electro-stimulator: Between October 2003 and March 2005, 158 experiments were performed on 20 women (86.4%) and 3 men with xerostomia: 10 patients in Berlin, 10 in Madrid, and 3 in Naples. All patients were Caucasian. The median age of patients was 61.5 years (range 28 - 79 years).

No significant negative side effects were observed during as well as after the experiments. Pre- vs. post-procedure changes in blood pressure and heart rate were clinically insignificant.

Wetness sensor data were available from part of the study due to downloading problems from the sensors to the PCs in several experiments. Figure 7 depicts the results provided by the wetness sensor.

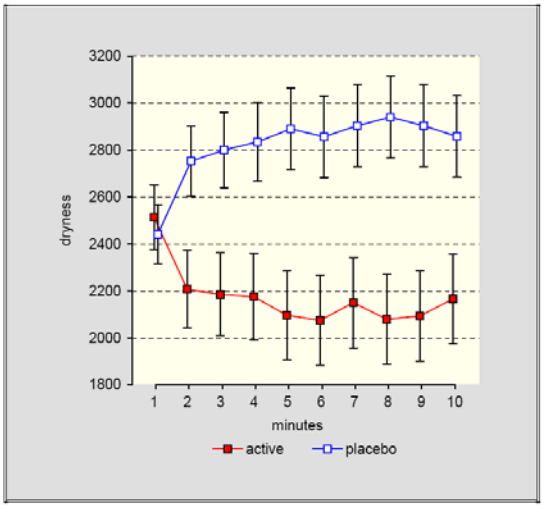

Figure 7: Means and SEMs of dryness in the course of 10 minutes active (n=49) and sham (n=59) stimulation

After one minute wearing of GenNarino, the registered dryness status was similar to sham and active modes. The mean difference over all 10 measurements shows a lower dryness following active as compared to placebo. The superiority of active was expressed by means of a highly significant interaction indicating a different time-effect-profile during both treatments: decrease of dryness while GenNarino is active and increase of dryness during the sham situation.

As to the subjective preference of active or sham, in total 38/158 (24.1%) experiments yielded no differences between active and placebo. In the remaining 120 experiments, active was preferred in 72 cases (60%) and placebo in 48 cases (40%) ($p<0.05$). Table 1 shows the results of the subjective perception of experimental results by the patients with special consideration of the order of active and sham tests. When the preferred mode was the first test, there was no significant difference between sham and active. However, the active mode was clearly the preferred mode ($p<0.005$) when the second test was chosen by the patients as the most effective one.

Table 1: Comparison of subjective perception of experimental results by the patients, considering the order of the modes - sham and active (n=158)

Patients' judgement (first vs. second test)				**p value***
Similar	**Dissimilar**			
	Preference	**The chosen test was on…**		
		sham mode	**active mode**	
24.1 %	first test better	13.9 %	12.0 %	n. s.
	second test better	16.5 %	33.5 %	p< 0.005

***** for sham vs. active comparison

Drug delivery device: A housing for the IntelliDrug device has been designed, to be placed on an intraoral device. Rapid prototyping parts have been

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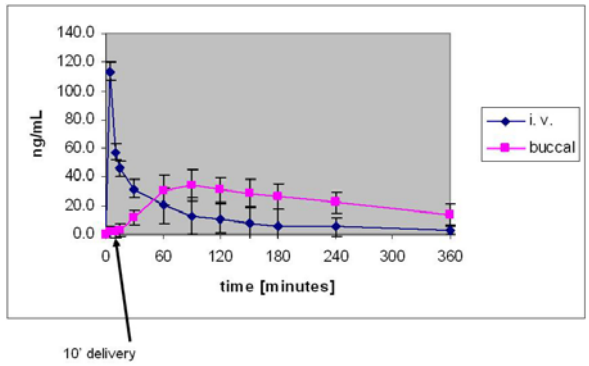
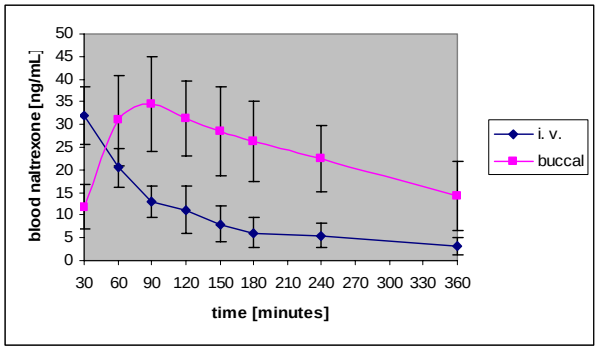
produced to demonstrate the size and the positioning and fixation of the housing in the oral device. Finite Element Method analysis was used to simulate the strain and the stresses induced by forces acting on the stainless steel housing. Preliminary electronics for the overall control of IntelliDrug sub-units and the necessary sensor circuitry have been designed and fabricated. A methodology for the bidirectional wireless transmission of data with a minimum power requirement and a draft communication protocol have been devised and implemented.

Administration of i. v. naltrexone induced a sharp increase in blood levels after 5 minutes, and then a steep decrease. In contrast, trans-mucosal delivery resulted in a gradual increase in blood naltrexone levels, reaching its peak after 90 minutes, and followed by a slow decrease. The first detectable levels of naltrexone after trans-mucosal delivery were registered at minute 5 in 7/14 cases and at minute 10 in 10/14 cases. In all time points there were statistically significant differences between i. v. and buccal, administration. After 6 hours the blood levels of naltrexone delivered to the buccal mucosa were significantly higher ($p<0.002$) compared to i. v. administration (Figures 8 & 9).





Figures 8 & 9: Naltrexone absorption into the blood stream following buccal delivery by the IntelliDrug electronic controlled system (pink curve) vs. intra-venous delivery (blue curve). The most relevant period - from minute 30 to 360- is shown. The vertical error bars denote standard deviation. Highly statistical significant differences between "buccal" and "i. v." were registered at every time point.

Discussion

Salivary electro-stimulator: Neural electro-stimulation of salivary gland function by application of electrical current, through the oral mucosa, on afferent nerve pathways receptors has been reported to increase production of saliva and to reduce the symptoms of xerostomia in patients with dry mouth due to several conditions [2, 3, 4]. It is believed that afferent nerves carry such impulses to the salivary nuclei (salivation centre) in the medulla oblongata, which, in turn, directs signals to the efferent part of the reflex leading to initiation of salivation. More recently, the use of extra-oral transcutaneous electric nerve stimulation (TENS) over the parotid gland was reported to effectively increase saliva production in healthy individuals, suggesting that TENS might directly stimulate the auriculo-temporal nerve that supplies secreto-motor drive to the parotid gland [5].

Because of absence of negative side effects, electro-stimulation theoretically overcomes the limitations of current xerostomia treatments and could represent a reasonable therapeutic option for dry mouth sufferers. In a first step of this project, preliminary data of salivation increase and symptoms relief after neuro-electrical stimulation of the lingual area of the mandibular third molar region, close to the lingual nerve path, were obtained using a removable device in a non-invasive test. No negative side effects have been recorded during and after the experiments.

Previous studies have demonstrated that oral mucosal wetness, expressed as thickness of the salivary film covering oral soft tissue surfaces, is an appropriate method for assessing the presence of the dry mouth condition, as it is a direct measurement of wetness of the mucosal tissues [6, 7, 8]. If saliva was evenly distributed throughout the mouth, it would present as a thin film of 72 to 100 µm thickness after and before swallowing, respectively, in interposition between two opposing surfaces of the mouth in contact. The Saliwell Study Group developed and validated *in vitro* an electronic sensor to obtain real-time recording of wetness changes during stimulation. Traditional salivary collection methods (spitting) were impractical due to the presence of the GenNarino device in the mouth.

The first wetness sensor signals were elicited after 1 minute of GenNarino wearing and their intensity were similar to sham and active modes, probably because of acute stimulation of mucosal mechanoreceptors by the device itself. However, thereafter a gradual differentiation process between the sham and the active modes evolved. In fact, a significant decrease of dryness was detected due to the intraoral presence of the GenNarino on active mode, as opposed to the effect of the sham device. It is known that the presence of an intraoral foreign body such as a complete denture *per se* acts as an additional mechanical stimulus in the salivary reflexes, initially augmenting secretion, followed by a decrease due to adaptation [9, 10]. As a consequence, the increase in

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dryness during the sham GenNarino wearing can be explained by the adaptation process of salivary glands to the presence of a foreign body. On the contrary, the decrease in dryness registered during the active GenNarino presence, means that electrical stimulation overcomes the feature of salivary glands described before.

The present study also shows a patients' preference of the active GenNarino over the sham one among the second tests, when those were selected as the most effective ones in relieving oral dryness. However, almost one third of patients (30.4%) reported sham tests having better effect than active. We think that the acute effect of mechanical stimulation might have confounded the subjective evaluation of oral wetness. As previously described, each experiment consisted of one sham and another active test, the order of which was not known to both patients and clinicians. Patients' memory could play a role in the selection, as more patients chose the second test (50%) over the first one (25.9%). Consequently, the ability of the patients to choose active over sham was greater the closer the test was to the moment of their decision.

Drug delivery device: The first studies of the IntelliDrug project have shown that naltrexone formulations do not request the addition of permeability enhancers for trans-mucosal delivery. On the basis of the results, naltrexone transfer through the buccal mucosa appears to be a passive permeation phenomenon. The biological process of buccal absorption involves a system in which naltrexone diffuses through the mucosal barrier, and the driving force of the movement is the concentration gradient. Since naltrexone, upon entering the cheek tissue distributes rapidly into a volume considerably large (blood stream), the drug concentration in plasma is maintained at low levels. The concentration, therefore, is lower than in the donor compartment (absorption site or mucosal surface) and the process is unidirectional and irreversible. Permeation starts when the concentration gradient is established and stops just when the naltrexone concentration approaches zero. Thus, after naltrexone dissolves and leaves the device in an almost saturated solution, it will reach the mucosal surface and passively permeates throughout the mucosa [11].

The porcine study demonstrated consistently different blood levels at each time point for buccal delivery compared to i. v. administration. Importantly, buccal administration lead to a more sustained blood presence of naltrexone than following i. v. injection. Yet, the appearance of naltrexone in blood was rapid, as well, since 5 minutes after delivery it was already detected.

To be effective in the treatment of drug addicts, blood levels of naltrexone should be kept constantly above 2ng/ml, a goal that can be reached simply by adjusting the release rate (dosage and timing) through IntelliDrug's micro-processor programming.

Conclusions

Embedding electronics inside intra-oral devices opens new horizons for novel applications, where the power of software and personal communication is harnessed to provide better and personal medical services at lower costs.

The salivary glands of xerostomic patients showed a good response to neuro-electro-stimulation by the GenNarino device. This had also a beneficial effect on the patients´ subjective condition. If chronically applied, neuro-electric stimulation could lead to a cumulative effect on salivary glands, determining a constant and lasting salivation, and a significant impact on the patient's quality of life. The results are encouraging to continue with the Saliwell project towards the next steps of testing the long range effect of GenNarino wearing and of developing and investigating the miniaturized stimulatory device mounted on a dental implant.

The results of the porcine study suggest that buccal delivery by an electronic system has the potential to cause long-lasting and controlled blood levels of naltrexone and other medications.

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MT – Promedt Consulting, St. Ingbert, Germany
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