

Increasing Drug Therapeutic Index: A u-health approach

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Abstract— An infusion has both therapeutic and side effects. Intra Venous (IV) catheters infuse drugs into the body and can also send back information on the effects of the infusion so that we can increase drug therapeutic index by controlling infusion parameters accordingly, thanks to Micrel Medical Devices micrelcare™ platform . This is an alternative way to trial phases of a drug, where its dose prescription is depending on the feedback reading and not based exclusively on age and weight .

I. INTRODUCTION

DNA interacts with drugs infused, and for some patients the drug is very well accepted (good DNA/drug interaction), while to others severe side effects are appearing.

“Pharmacogenomics (Wikipedia) is the branch of pharmaceuticals which deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity. By doing so, pharmacogenomics aims to develop rational means to optimise drug therapy, with respect to the patients' genotype, to ensure maximum efficacy with minimal adverse effects. Such approaches promise the advent of "personalised medicine", in which drugs and drug combinations are optimised for each individual's unique genetic makeup.”

Till the advent of DNA screening and drug interactions study era, a realistic approach to personalized medicine is described herein.

II. DRUG INFUSION AND SIDE EFFECTS

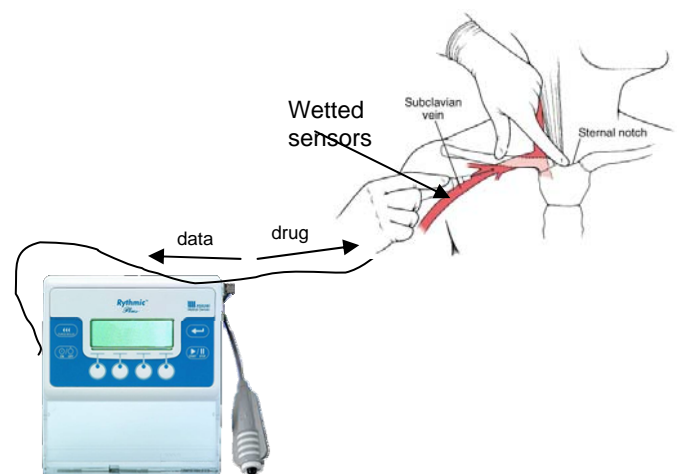
Walking patients are receiving drugs with ambulatory pumps like Micrel Medical Devices' Rhythmic™ pump having an integrated drug reservoir. Today's practice is the infusion parameters to be programmed on the pump according to patient's weight, age and genre. Sometimes it happens a patient to deviate from the above prescription rule and suffer severe side effects. All drugs are toxic over a certain concentration in blood for a given patient. The problem is to find the overdose limit for each patient at

special living conditions of the moment of infusion. Where “overdose” is the drug concentration in the blood or on injection site which is just above safe limit. We have been reported an old lady to have received the correct infusion parameters for PCA –morphine infusion according to her weight and age, the pump had correctly administered the dose profile, but the lady became bluish after some time; she was an exception to the prescription rule found by clinical trials during drug approval process.

Drug interaction when used simultaneously, is another important cause of overdose.

Insulin infusion side effects and difficulties to glucose prediction are very well known, due to their dependence not only on the internal mechanism of glucose-insulin metabolism but also on a great number of life style factors, like carbohydrate contents of daily meals, physical activity and exercise, stress, other diseases, etc. Continuous real-time measurement of glucose, less- and non-invasive, as well as the closed loop control of insulin infusion, is searched everywhere in academia and industry.

But the biggest challenge of the system we describe herein, is to control the therapeutic index of dugs that could not be placed on the market with conventional methods of today.



It becomes then obvious that if we can observe/measure

the side effects by a return route while we infuse a drug, we can then

- Prevent casualties caused by medication error
- Allow a drug with side effects to be tried on a patient and by reducing or stopping infusion before side effects appear find the toxic limit for the patient's genotype.
- Allow drugs that have metabolic effects depending on living conditions (like insulin) to be administered safely.

III. PROGRAMMING WITHIN LIMITS

Our Rhythmic™ pump has the ability to let the nurse or an automatic pump process, or a distant server, change certain infusion parameters within predefined limits, while these limits can also be changed by the doctor over the web by a safe telemetry process described below. So today's practice is nurse to trim infusion parameters within these limits to maximize therapeutic effects and reduce to minimum side effects as for instance in PCA.

The pump itself can use, advanced modelling techniques based on artificial intelligence methodologies [26, 27] and control theory, to trim these parameters within same predefined limits, if sensors report infusion effects as shown above; this is called closed loop infusion [28]. The method we use to let medical personnel rely on the automatic process, is the "trimming within limits" process preset by doctor [29]. The pump being a class IIb medical device is considered reliable to observe these limits and so excessive over or under-infusion can be prevented.

The sensors placed in the implantable catheter tip [22-24] used in many chronic diseases, or post operatively, send data back to the pump. Sensors like ECG /arrhythmia detector and pulse oximeter [25] can be wearable on the chest or behind the ear.

In complicated algorithm cases or in case the pharmaceutical company needs to keep the closed loop algorithm proprietary, the algorithm can be located in a server under their control and output communicated to the pump through telemetry. Proprietary algorithm has been the case in the past where a pharmaceutical company put the algorithm in an electronic chip and gave it to pump manufacturers willing to infuse their drug.

IV. MICREL CARE™ SERVICE

MicrelCare™ is a telemedicine service based on GSM/GPRS telemetry connecting our ambulatory Rhythmic Connect™ pump and sensors to our www.micrelcare.net server [1-3]. The server web pages are organized by Home Care Provider/Hospital service and have data on patients treated and nurse personnel organized in nurse groups. So a

nurse actually in charge for a patient will receive an SMS with problem encountered with the pump or the treatment, or informed that in x time she has to go to replace the drug reservoir. Doctor and paramedics can watch infusion (events and graphs) and therapy progress real-time on the web per patient, starting from a list of the patients with alarms in red popping up in the list.

Technically this is possible as follows: Our Rhythmic Connect™ pump is connected serially with our IP-Connect proprietary mobile GSM/GPRS data phone, permanently connected with our micrelcare server, while also communicating by radio link, like Bluetooth but ultra low power [1], to other personal health devices on the patient, in form of a Personal Area Sensor Network. We develop a miniature ECG pulse rate and arrhythmia analyzer wearable on a conductive tissue belt on chest, and a pulse oximeter behind the ear [25], similar to hearing aids, measuring from the ear lobe.

Micrel Medical Devices holds European and US granted patents for this technology [3].

It is known that Micrel technology has eliminated all annoying air-bubble alarms from all our models.

When a pump is connected, some alarms needed from EN60601-2-24 standard are preferably sent to nurse by SMS instead of annoying the patient who most of the times does not know what to do with alarms. This is in line with Micrel philosophy of an "alarm free" therapeutic system for mobile and home patients.



Sensors for side and therapeutic effect feedback we work on [4-21], can measure:

- Central Venous Pressure, Temperature,
- pO₂ and pCO₂ via polarographic (CHEMFET) or fiber optic –extracorporeal analyzer
- pH, ions (K⁺, Mg⁺, etc.) via ISEs and ISFETs

- protein & DNA detection using biosensors with enzymes or whole cells
- Glucose and ketones for in vivo blood analysis, using a small size Raman spectrophotometer under development in collaboration with University of Crete.

As GSM networks can have discontinuity in the data flow (the pump sends status every 10 minutes and events immediately), the data are stored locally and pushed onto the server when communication is reestablished. In case of closed loop, local intelligence /decisions can fill the gap, always within referred predefined limits [30].

The safe programming over the web is accomplished by a number of steps. First the nurse in charge to validate on the patient the pump S/N -to- patient name link and therapy prescription; the validation is done through the pump itself, where patient name appears on the pump coming from the server. Second, each doctor demand has a mirror reply shown on web coming from the pump, to assure good reception, a safety additional to data CRC. Third, when doctor acknowledges the data integrity as above, he then validates the programming and the pump can start. Doctor and nurse have passwords as a key to “who did what when” reporting system.

The system totally ambulatory for working and normally living patients as an ICU on the move, has the power to change the way drugs are registered, and even revitalize drugs rejected from clinical trial process.

V. DRUG CLINICAL TRIALS

Drugs are rejected during the clinical trial phases if some patients –not the majority- experience severe side effects due to the different drug /DNA interaction. But a rejected drug could very well be beneficial to other patients that their genotype can admit the drug without scaling to side effects.

In case of pump infused drugs, if we could measure the side effect itself, vital signs, or a blood parameter level that forebodes the side effect, we could (using a stand alone or web based system) reduce drug infusion to just below overdose, so that we have the maximum therapeutic index for a given patient.

A more difficult and sometimes more effective way is to watch the metabolic effects of the drug in a living body cell, but this is basic research project.

Micrel Medical Devices is willing to tailor per application the system, working closely with pharmaceutical companies from the design phase of clinical trials. Select together sensors to report therapy, so that in the event that a drug cannot be approved by the standard statistically based way, there are enough data from sensors we used during clinical trials, to continue trials with controlled infusion per patient

(closed loop) using our powerful technological platform. Additional or different sensors may be needed when knowledge on drug side effects is increased.

Then commercially, it is possible to find the drug’s toxic limit for a given patient’s genotype, using the Rythmic Connect™ Pump and MicrelCare™ platform for a limited time. After that, it is possible to use the drug without monitoring on the same patient at below his own toxic limit.

VI. CONCLUSION

Micrel Medical Devices are experts in ambulatory infusion, our pumps have outstanding connectivity and ease of use, alarm-free operation for home care and powerful mix with tele-reporting and tele-controlling make them ideal candidates for a novel way of delivering drugs to normally living patients, in an ubiquitous health approach, reducing side effects and increasing drug therapeutic index.

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