

IDOL project

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Final report

Contents

Background	2
Goals.....	3
Original objectives	3
Modifications of original goals	3
Activities and results	4
Analysis of data from previous studies	4
The PEDAL study	5
The test battery	6
The decision support system	7
The prediction model	8
Courses	8
Thesis work	9
Future plans	9
Collaboration with industry.....	10
Collaboration with education	10
Collaboration with other research groups	10
Information and communication	10
Economy.....	11
Evaluation.....	11
References	12

Background

Parkinson is a slowly progressive neurological disease. It affects a small area of cells in the mid-brain, vital for motor function control. Standard treatment at the initial stage of the disease is levodopa/carbidopa in tablet form, aimed at restoring depleted dopamine levels. Medication must be individually tuned; under dosing does not relieve the symptoms and overdosing leads to side effects with uncontrolled movements (dyskinesias). The dosing also must be adjusted daily with respect to food intake, exercise and mood. The interval for the best dose shifts upwards and gets narrower as the disease progresses.

Levodopa has a half-life of ca two hours and is absorbed in the small intestine. This causes problems when stomach emptying is irregular. In advanced Parkinson, improvement can be achieved with intestinal infusion of a levodopa/carbidopa gel (Duodopa®) compared with tablets [1, 2].

Administering Duodopa® is complex and requires special training of clinical staff and patients. For new candidates, the treatment is tried-out using a nasal tube. Initial pump settings are calculated based on previous tablet dose and are adjusted on the basis of after-dose response (state) during some days in the hospital. Typically, the pump is shut off at night. The day starts with a morning bolus dose to reach steady state and a continuous flow rate is supplied thereafter. In addition it is possible to take extra doses if needed depending on food intake etc. Since Parkinson is a progressive disease, there will be a need to follow up on the treatment over time.

IDOL, “Intelligent Duodopa On-Line”, or “decision support for medication in advanced Parkinson”, has been a three-year project (from 2003 to 2005) sponsored by the Knowledge Foundation in collaboration between Högskolan Dalarna, Uppsala University, NeoPharma AB and Pharma Consulting Group AB (replacing Clinitrac AB who went bankrupt in July 2004). The project’s work group has consisted of Mark Dougherty, Högskolan Dalarna, project leader, Torgny Groth, Uppsala University, Bo Johansson, Högskolan Dalarna, and Jerker Westin, Högskolan Dalarna. Students at the master program in computer engineering, Högskolan Dalarna have also been involved. The board has consisted of Torgny Groth, chairman, Mark Dougherty, Stefan Åsberg, NeoPharma, Henrik Blombergsson, Pharma Consulting Group and Alan Yeomans, Neptunus Data AB. The project has had a reference group consisting of Sven Pålhagen, Karolinska University Hospital Huddinge, Patrik Eklund, Umeå University, Mats Karlsson, Uppsala University, Dag Nyholm, Uppsala University Hospital, Jan-Olof Olofsson and Bertil Jöhnemark, Parkinson patient organisation Dalarna.

Goals

Original objectives

In the original project application and project plan, the following goals were formulated: The overall objective was better treatment for patients with severe Parkinson through helping the medical doctor to make quick and accurate decisions concerning Duodopa® dosage. This will be achieved through design and development of a decision support system based on on-line patient diary assessments. Such a decision support system will be particularly useful in regional hospitals, where often the doctor making the dosage decision is not a specialist in Parkinson. Note that since Parkinson is a progressive illness, dosage decisions have to be regularly reviewed for each individual patient. Thus the system would be used many times over for every patient. An industry objective was good publicity and evidence that duodenal administration works well together with the DSS so that more patients get access to the treatment. A HEI objective was competence development at Högskolan Dalarna through research education for staff and through collaboration with relevant industry and academic partners.

Measurable project deliverables were:

- i) Delivery of a prototype decision support system.
- ii) Presentation of 2 papers at international conferences.
- iii) Publication of at least 2 articles in refereed international journals.

Product goals were:

- i) The decision support system should be easy to use for both doctors and patients.
- ii) The number of questions for the patients to answer and necessary actions by the doctor should be minimised.
- iii) The knowledge base and algorithms should use "state of the art" medical decision support system technology.

Modifications of original goals

Clinitrac's bankruptcy led to development of an entirely new e-diary system and this took time from other project activities. The test battery described below has a pending patent and thus, it was not possible to publish details during the project. Communication with the current Duodopa® pump was not possible since the manufacturer (a third party, not in the project) would not supply necessary documentation of the communication interface. Therefore only an off-line demo of the decision support system could be produced.

The project has taken a bit broader approach compared to the original goal description and has worked also on other issues related to decision support concerning Duodopa®. Our definition of decision support has been:

- i) *How do we best select treatment?*
This is described in the sections on data analysis and the prediction model below.
- ii) *How do we best initiate a new patient?*
Initial dose calculations were added in the decision support system. We started development of a pharmacokinetic- pharmacodynamic model that can be used for training purposes and simulation experiments about how to quickly reach steady state.
- iii) *How do we evaluate treatments?*
This issue led us to develop the test battery.
- iv) *How do we detect problems and how do we deal with them?*
These issues were dealt with in the decision support system demo.

Activities and results

Analysis of data from previous studies

The first part of the project concerned data analysis of two previous studies with Duodopa® [1, 2]. The first objective was to investigate possibilities to build a pharmacokinetic-pharmacodynamic (PKPD) simulation model based on the data from the first study [1]. It turned out that existing data were unsuitable for this purpose, since levodopa plasma concentrations available were always around their optima. In order to identify model parameters, both high and low concentrations are required. This prompted us to plan for and initiate a complementary study for PKPD modelling, PEDAL, further described below.

Other findings from explorative data analysis of this study were indications that often too small extra doses had been given, since many times there were no visible increase in plasma concentration shortly after taken extra doses. Another finding was that in the first study, fluctuations while on Duodopa® were strongly correlated with years on levodopa. This correlation was not found in the second study [2]. However, in the second study many patients were prescribed an SSRI-type antidepressant. If the patients with SSRI were removed from analysis, the correlation was present also in the second study, indicating a possible relation between SSRI and fluctuations and/or rate of progression.

Further, correlations were found in both studies indicating that patients with more severe symptoms at baseline were most improved after infusion. This finding led to a prediction model and a submitted publication described below [3].

A finding in the second study where patients had both diary assessments and clinical ratings of motor function was that correlations between these were low. Significant improvement with Duodopa® was seen in both diary answers and clinical ratings. Hence, patients and doctors agreed that there was improvement with Duodopa®, but the magnitude of the perceived improvement according to the diary and improvement according to the rating of motor function differed. This led us to the idea to combine e-diary questions with on-screen motor tests in a test battery to capture both aspects of patient state. Some of the original diary questions gave highly correlated answers and could be removed. We also found that one week with a home diary was sufficient time to yield useful results. The test battery we developed is further described below.

Posters describing data analysis results were presented at “The Movement Disorder Society's 8th International Congress of Parkinson's Disease and Movement Disorders” in Rome [4] and at “The 16th International Congress on Parkinson's Disease and Related Disorders” in Berlin [5].

The PEDAL study

PEDAL stands for Parameter Estimation for a model for Duodenal Administration of Levodopa. The main purpose of this clinical study was to estimate a pharmacokinetic-pharmacodynamic model for Duodopa® that can be used for training purposes: One can simulate the distribution of the drug and to some extent the probable effect based on different settings of Morning dose, Flow rate and Extra dose. PKPD based on oral levodopa is problematic because of irregular gastric emptying. With Duodopa® we think we will get less random variation. Other objectives were to study the absorption of Duodopa® over the gut wall and to form a basis for power calculation for future larger study.

PEDAL involved three patients already on Duodopa®. Treatment started in the morning after a washout during night. Data collection started in this stage of low levodopa levels. Normal morning dose plus 50% was then given and data collection continued until the clinical effect was back at baseline, or after at most four hours. Then the normal infusion rate started. Data collection continued for another two hours. The procedure was repeated on two occasions (non-consecutive days) per patient. One patient only had one visit. The following data were collected in 5 to 15 minutes intervals:

- i) Accelerometer data from the ActiGraph biosensor.
- ii) Diary data from the Clinitrac electronic diary. Three questions about ability to walk, feelings of “off” symptoms and feelings of “dyskinetic” symptoms.
- iii) Clinical assessment of Parkinsonism and dyskinesia in the form of a rating by a physician as in [2].
- iv) Plasma concentrations of levodopa, carbidopa and a levodopa metabolite (3-O-methyldopa).

We had plans to combine the plasma analysis with microdialysis in adipose tissue (second compartment) in PEDAL but this was not possible to arrange.

In the framework of the IDOL-project, the study was designed and necessary GCP documents were produced. The study was accepted by the ethics committee at Karolinska Institute and the clinical work was performed in collaboration with Sven Pålhagen, Huddinge. Lab analyses of the plasma samples are currently being performed by Quintiles in Uppsala and modelling work will commence when the concentration data become available. There is also an ongoing study at Quintiles testing long-term stability of levodopa at low temperatures.

Some preliminary modelling work has been done: Simulation experiments with data in [6] suggested that levodopa infusion pharmacokinetics can be described by a two-compartment model. Literature studies and simulation experiments led to a hypothesis for an effect model incorporating fluctuations in addition to concentration-related fluctuations, based on the following assumptions: *“Dopamine exists in two different pools; active dopamine in and near synapses, and stored dopamine in vesicles in neurons. Dyskinesias are due to conversion of levodopa to active dopamine in extra-cellular space and limited storage capacity. The demand for active dopamine is varying. Progression of Parkinson causes both decreased intracellular levodopa production and storage capacity due to cell death. Probably receptor plasticity and mood-related dopamine release must also be taken into account.”*

The test battery

Evaluating status in patients with motor fluctuations is complex and occasional observations/measurements do not give an adequate picture of time spent in different states. Analysis of data from [2] gave cause to believe that motor tests will add aspects about disease state, not captured by a diary alone. Further, the bankruptcy of Clinitrac forced us to develop a new e-diary system.

A Swedish patent application [7] was filed in February 2005 and an international application (PCT) was filed in February 2006. The invented test battery consists of a combined e-diary with Parkinson-related questions and on-screen motor tests (different tapping tests and spiral drawings). In fluctuating patients, it should typically be used several times daily in the home environment, over periods of about one week. The aim of this test battery is to provide status information in order to evaluate treatment effects in clinical practice and research, follow up treatments and disease progression and predict outcome to optimize treatment strategy.

An evaluation with two pilot patients was performed before and after receiving new treatments for advanced disease (one received Duodopa® and one received DBS). Speed and proportion of missed taps were calculated for the tapping tests and the sample entropy of the radial drawing velocity was calculated (using the SampEn algorithm) for the spiral tests. Utilisation of this algorithm was quite complex, especially since it was needed to filter out problems caused by the pointer accidentally lifting off the screen or one of the other fingers of the patient causing false data points. Test variables were evaluated using non-parametric statistics. Results were that post-treatment improvement was detected in both patients in many of the test variables. A poster abstract was submitted to the “10th Congress of the European Federation of Neurological Societies” in Glasgow [8].

The test battery is currently being evaluated in a long-term health economics study with Duodopa®, DAPHNE (EUDRA S187.4.001). The study will progress over three years and will include about seventy patients at nine clinics in Sweden. During the first year, the test battery will be used one week every third month and during years two and three, one week every sixth month. The patients respond to questions and perform tests in the home environment four times daily during test weeks. As of today, four patients have been included in the study.

The decision support system

A demonstrator of a web-based decision support system (DSS) for Duodopa® was constructed using a rule-based fuzzy inference system (FIS) based on expert-generated rules. The system generated dose advice based on patient states shortly after taken doses. Mapping between staff and patients, alerts of unusual or unwanted states and dosing and advice on dose adjustments of typical doses are examples of included functionality. A typical scenario is: login; see the list of patients and periods and most recent alerts. Subsequently the user selects a patient and period and can check dose and state statistics and pointers to possible alerts and suggested dose adjustments. Going further, one can compare different periods graphically and access detailed data via time series plots. Definition of requirements was done by interviewing a few experienced users and letting them evaluate user interface prototypes.

Development was done according to a linear model with added iterations to define the user interface requirements and tune the FIS:

- i) **Analysis:** This phase involved acquiring a general understanding of the problem, extracting knowledge from data and formalizing the expert knowledge.
- ii) **Design:** The overall architecture involved database design, class design, FIS design and user interface design. The system was designed as a three-tier architecture: front-end was the user interface (web-application), middle-ware was the DSS and the back-end was the database. All business logic, FIS and calculations were implemented in the middle-ware. Object oriented design and programming were used to develop the system.
- iii) **Construction:** A business level was created with object oriented programming to generate summaries of alerts, states and doses. In the FIS for calculating new doses, all values of doses and states were treated as fuzzy variables that were described by a fuzzy set. Fuzzy rules based on a domain expert's experience were implemented to carry out evaluations and "crisp" values (new advised doses) that came out after firing rules were stored into the database.
- iv) **Testing:** To get minimal mean absolute error compared to actual taken doses for design data the parameters of the membership functions in the fuzzy inference system were tuned. One data set was used to develop and tune the FIS and another was used for evaluation. Several iterations of the user interface were done.

An evaluation showed that overall goodness-of-fit (R^2) between advised and taken doses for design data (new patients, see below) was 0.65 and for evaluation data (ongoing patients, see below) it was 0.98. The worse performance in the new patients can be explained by the fact that the rules were designed for ongoing patients, usually needing only minor adjustments.

Design data for the DSS were provided by NeoPharma AB. Data consisted of dosage and status information from new Duodopa® patients and were collected from April, 2002 to October, 2004 for 16 patients, observed between one and six consecutive days. Patient states were defined by clinical examination of motor function of a standardized sequence of motor tasks. Global state was noted on a discrete integer scale from -3 to +3 where negative values represented Parkinson symptoms due to too little medicine and positive values represented side effects due to too much medicine. This scale is further described in [2]. Evaluation data were taken from the DireQt study [2]. Only the days when the patients were on Duodopa® were used as evaluation data. In this case, doses had already been stabilized at the time of data collection.

The original plan was to produce an on-line prototype of the decision support system. Since the pump manufacturer would not supply us with necessary specifications of the communication interface, we have been unable to read data from the current Duodopa® pump from our test battery. In any case, it would have been problematic with connecting the two units, since the current pump had no interface for wireless communication and cable connections would be impractical for Parkinson patients and may pose a potential electrical security problem during battery charging. Requirements on the next generation pumps would be a wireless communication interface and an API to access dose-events. Another issue with the current pump was that it had a limited memory space that lead to dosage data being overwritten unless being regularly manually downloaded to a PC.

In a future version of the system, the plan is to assess patient state on the -3 to +3 scale by combining test battery results in an expert FIS. A paper describing the DSS demo was submitted to the “23rd annual workshop of the Swedish Artificial Intelligence Society” in Umeå [9]. The demo can be accessed at <http://193.11.77.85:8500/newDSS/> login: *admin*, password: *admin*.

The prediction model

Further analysis of data from [1, 2] was performed to find predictive factors related to degree of improvement with infusion. Pearson correlation coefficients between measures of improvement and baseline variables were calculated. Using data from one study, a prediction model was designed and was then evaluated using the other study’s data. Correlations were found indicating that patients with more severe symptoms at baseline were most improved after infusion. It was found that a linear model relating baseline severity to improvement was adequate. Statistical tests estimating random effects (regression to the mean) showed no significant impact. Goodness-of fit (R^2) of the prediction model based on baseline total UPDRS was 0.46. Results should be verified in a prospective study. This paper was submitted to Parkinsonism & Related Disorders, 2005 June and resubmitted with revisions 2006 February [3].

Courses

In addition to project work and literature studies, Jerker Westin has completed the following PhD courses during the project:

Högskolan Dalarna:

- i) Neural Networks and Fuzzy Logic 5 p D
- ii) Medical Decision Support Systems 5 p D
- iii) Data Mining 2 p D

Uppsala University:

- i) Clinical Pharmacology 1 p
- ii) Neuropharmacology 5 p C
- iii) Introduction to Scientific Research 5 p

University Halle-Wittenberg:

- i) Pharmacokinetic and Pharmacodynamic Modeling with ADAPT 1p

Learning Tree:

- i) Object oriented analysis and design 1 p

Thesis work

The following 20 weeks Master thesis work in computer engineering, supervised by Jerker Westin, has related to the project:

- i) Mobyen Uddin Ahmed, A web enabled fuzzy rule-based decision support system for dose adjustments of Duodopa infusion to patients with advanced Parkinson's disease, HDa E3244D, 2005. *Has contributed to a submitted research publication* [9].
- ii) Sridhar Koleti, Motor tests on a hand-held computer for assessing state of patients with Advanced Parkinsons disease, HDa E3168D, 2005.
- iii) Shahina Begum, Modeling fluctuations in advanced Parkinson's disease using statistical and soft computing methods - data mining for contributing factors, HDa E3166D, 2005. *Has contributed to a submitted research publication* [10].
- iv) Praveen Kumar Yerramsetty, Data mining for factors that influence the degree of improvement of duodenal infusion of levodopa over standard treatment in patients with advanced Parkinson's disease, HDa E3095D, 2005. *Has contributed to a submitted research publication* [3].

Future plans

In the finished project, IDOL, a prototype test battery for evaluating status in patients with fluctuating movement disorders and a decision support system demo were developed. In a proposed new project, MOVISTAR, we wish to further develop the test battery and validate it in clinical studies. In addition, we would like to build a common platform for the next generation pumps (Duodopa® and apomorphine) including a useful web based decision support system, based on both patient state and dose information. The main tasks will be software development, validation in clinical studies and analysis of data using advanced AI tools.

Collaboration with industry

NeoPharma AB was a partner in the IDOL project and has been bought up by Solvay Pharmaceuticals GmbH. Solvay intends to continue and expand the collaboration with our research group. Pharma Consulting Group took over as project partner after Clinitrac's bankruptcy. The involvement of Pharma Consulting Group was smaller than originally planned since we did not build a Parkinson registry in the framework of the IDOL project. They did provide help with statistical consulting. Nordforce Technology AB and Umbilicus Nordica AB have been involved in the IDOL project as sub contractors to NeoPharma. There has also been links to former Clinitrac staff in different locations after the bankruptcy. Contacts have been taken with InfuCare AB who also has an infusion treatment for PD and has similar needs for status and dosage monitoring as Solvay. Overall, industry collaboration has been vivid, open-minded and fruitful in this project.

Collaboration with education

In the IDOL project, computer engineering undergraduate students have done a project as part of a B-level course in collaboration with HEIs in Åland and Finland, trying to incorporate decision support in the previous patient diary system by Clinitrac. One C-level (undergraduate) and four D-level (Master program) thesis workers have done projects related to IDOL (see Thesis work above). One additional student doing a D-level thesis is ongoing.

Collaboration with other research groups

The project has strong links to both Uppsala University (Torgny Groth, biomedical informatics and engineering/dept medical sciences; Dag Nyholm, neurology/dept neuroscience; and Mats Karlsson, pharmacokinetics and drug therapy/dept pharmaceutical biosciences), Uppsala Academic Hospital (Dag Nyholm, clinics of neurology and rehabilitation) and Mälardalen University (Peter Funk, dept computer science and electronics). At Karolinska University Hospital Huddinge the project has a close established cooperation with Sven Pålhagen (senior medical doctor with specialisation in neurological disorders). At Umeå University the project has a link to Patrik Eklund (dept computer science).

Information and communication

A popular science TV program about this research has been produced and will be broadcast in SVT Knowledge channel in March or April 2006. The project has had patient organisation representatives on the reference group and communicated results to them. Work has been presented at two international conferences and at two meetings arranged for clinical study investigators. Results were also communicated at research days at Högskolan Dalarna.

Economy

The financial report is attached as a separate document. We were unable to get the financial report from Clinitrac who went bankrupt in 2004. We believe they spent at least the SEK 220 000 they planned to spend on the project.

Evaluation

This report shows clearly that this project has been planned in a dynamic way. The initial stated goals have been refined and modified as work has progressed. However, it is our opinion that the plan for any research programme must be dynamic and respond to both external events and also the knowledge gained as the project proceeds. Although much of the need for dynamism is driven by a desire to make the results of the project useful to industry and society, it can nevertheless make it somewhat harder to judge the overall success of the project.

Key evidences for the success of the project are:

- the enthusiasm which the pharmaceutical industry has shown for our work: not only the project partners but other companies have been interested in participating in both this project and also future projects.
- the patenting of the test-battery (even though this was not quite what was described in the original goals of the project)
- our success in integrating the research project into the teaching environment of Högskolan Dalarna
- the good level of publication and communication activities. Note that more publications will emerge from the project, given the natural time-delay between performing research work and publishing it in scientific journals
- the willingness of Parkinson disease patients to help in the research and the enthusiasm they have show when we have described the technology we are developing.
- the fact that four of the project participants have started a company, Jemardator AB in order to exploit the patented results. This company already has a contract worth approximately 500,000 SEK for licensing the technology it has intellectual property rights over.

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