Optimised dose titration for Duodopa treatment based on simulation experiments – implementation in a decision support system
Abstract

The aim of this work was to design a set of rules for levodopa infusion dose adjustment in Parkinson’s disease based on a simulation experiments. Using this simulator, optimal infusions dose in different conditions were calculated. There are seven conditions (-3 to +3) appearing in a rating scale for Parkinson’s disease patients. By finding mean of the differences between conditions and optimal dose, two sets of rules were designed. The set of rules was optimized by several testing. Usefulness for optimizing the titration procedure of new infusion patients based on rule-based reasoning was investigated. Results show that both of the number of the steps and the errors for finding optimal dose was shorten by new rules. At last, the dose predicted with new rules well on each single occasion of majority of patients in simulation experiments.
Contents

1 Background ..................................................................................................................1

2 Objective ......................................................................................................................2

3 Method ........................................................................................................................3

  3.1 Data calculation .........................................................................................................3

  3.2 Data selection .............................................................................................................4

  3.3 Data analysis .............................................................................................................5

  3.4 Rules construction ......................................................................................................6

  3.5 Test and decision support system design .................................................................9

4 Results ..........................................................................................................................10

  4.1 Calculation results ...................................................................................................10

  4.2 Bland-Altman plot .....................................................................................................11

  4.3 Titration rules ...........................................................................................................16

5 Test ................................................................................................................................18

6 Conclusion ....................................................................................................................24

7 Discussions ..................................................................................................................25

8 Future work ..................................................................................................................26

9 Acknowledgement ........................................................................................................27

10 Reference .....................................................................................................................28

11 Appendix I: Code for calculating FR in +2 condition .............................................30

12 Appendix II: Code for decision support system .........................................................32
1. Background

Duodopa is a levodopa/carbidopa gel. Nowadays Duodopa is spread used for Parkinson’s disease. Unfortunately, with increased dosing and prolonged use of levodopa, PD patients experience side effects including dyskinesias (spontaneous, involuntary movements) and "on-off" fluctuations when the medication will suddenly and unpredictably start or stop working. But too low dose will not have relief to PD patients. In this patients group, finding the interval for optimal dose is arduous and tablets cannot make medicine levels stable enough. This situation can be improved with infusion of medicine directly into the intestine via an adjustable pump. The pump is start with a morning dose during the days and disconnected at bedtime but tablets are available to manage troublesome night-time symptoms if needed. The problem is how big the infusion dose should be changed when the symptoms appear and the time of making level stable should be as soon as possible.

A population pharmacokinetic-pharmacodynamic (PKPD) model [5] had been estimated from data in clinical studies. It would be used in the infusion dose calculating function in different conditions.
2. Objective

In this research, medicine Duodopa was used. A set of rules will be designed for levodopa infusion in Parkinson’s disease based on a simulation experiments. In earlier research, a simulation experiments were investigated by using the same database. Thus the data utilizing in this research should be depended on the simulation experiments. A set of rules for titration procedure need to be investigated and compared with current practice. The new rules should be more quickly than current practice and less error when finding the optimal dose. Meanwhile the new rules should be suitable for tolerant and sensitive patients when testing in simulation experiments. A decision support system for judging infusion dose has to be investigated. In new patients, the goal is to reach optimal dose as quickly as possible, minimizing both over and under treatment in all types of patients based on rule-based reasoning.
3. Method

3.1 Data calculation

The infusion dose was calculated by the simulation experiments. The conditions of E value has minimum of -3 (severe PD symptoms) and maximum of +3 (severe dyskinesias), and target should be zero. [5] The infusion dose difference was calculated in between conditions and optimal dose (target 0). Function in simulation experiments with Runge–Kutta (RK4) [7] method, the dose was got. The system error here is 0.2. The scale is 0.2 lower in right level. The interval here is [-2 +2]. So we have -1.8 -0.8 +0.8 +1.8. Taking little overshoot treatment in account, this error is good for treatment.

The calculation procedure for infusion dose:

Select conditions reasonable patients in simulation experiments’ database. For example if patients in +2 condition were needed, the patients with the parameter EMAX+BASE>=2 was chosen from simulation experiments’ database.

By running the Runge–Kutta algorithm, the infusion dose might cause +2 condition was got.
3.2 Data selection

Data selection was next procedure. The reasonable data from patients who have at least three conditions was selected for analyzing. For real life analysis, the conditions +3 and -3 practically have fewer patients in these two levels. Those are ignored. For the influence from BASE+EMAX in formula, some patients BASE+EMAX cannot reach to +1 or -1, so they only have one condition or two conditions. These patients who only have two conditions or less should not be considered for first analyzing. The rest of the patients can be utilized for test the rules. The reason is for more conditions can help data with more effective. It can be tested in more conditions with different infusion dose in the same patient. The result we got from this method can be credible. If make some improvements in results, the data may be chosen as many as possible.

On the other hand, these patients who have more conditions could be simulated at different condition level in the simulation experiments. Two hundred and sixty six patients have been chosen. The infusion dose at five condition levels will be found after doing the simulation. Change infusion dose for every selected patient in simulation experiments.

Example: Patients ID 148, 152, 154, 156, 157, 159 were chosen from ID 148 to 159.

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</table>

Figure 1 data selection table

Example for Patients ID chosen

Finally, 266 patients were chosen from database.
3.3 Data analysis

Now, we have two hundred and sixty six patients for finding the titration rules. We display all the data in excel file and find the common sense between target 0 and each condition. Find how far from each condition to target 0. Organize the difference, and calculate average distance between target 0 and each condition. Thus, the general rules were first found by calculated the average of the difference. A set of rules also be discovered by observing from the display table.

Infusion dose will be described as fr.

General rules:

I. if we see +2 then decrease 0.3
II. if we see +1 then decrease 0.2
III. if we see -1 then increase 0.1
IV. if we see -2 then increase 0.2

Observing rules:

I. fr $\in [0,1.5]$ decrease 0.2 fr $\in [1.5,3]$ decrease 0.4
II. fr $\in [0,1]$ decrease 0.1 fr $\in [1,2]$ decrease 0.2 fr $\in [2,3]$ decrease 0.3
III. fr $\in [0,2]$ increase 0.1 fr $\in [2,3]$ increase 0.2
IV. fr $\in [0,1]$ increase 0.1 fr $\in [1,2]$ increase 0.3 fr $\in [2,3]$ increase 0.4
3.4 Rules construction

Optimized rules:

We first calculate the difference between target 0 and each condition after changing fr by using general rules and observing rules. The result in distance from after changing and target 0 not seems so ideal. So after calculating the difference between target 0 and each condition, we found fr in different interval affect the difference. If we divide fr interval into some small interval for instead, the result seems so better.[8] Therefore we optimized our rules as follows:

I. if we see +2 and fr ∈ [0,1] decrease 0.1 or fr ∈ (1,2) decrease 0.3 or fr ∈ [2,3) decrease 0.4 or fr≥3 decrease 0.5

II. if we see +1 and fr ∈ [0,1] decrease 0.1 or fr ∈ (1,2) decrease 0.2 or fr ∈ [2,3] decrease 0.3 or fr>3 decrease 0.4

III. if we see -1 and fr ∈ [0,2) increase 0.1 or fr ∈ [2,3] increase 0.2 or fr>3 increase 0.3

IV. if we see -2 and fr ∈ [0,1] increase 0.1 or fr ∈ [1,2] increase 0.3 or fr ∈ [2,3] increase 0.4 or fr>3 decrease 0.5

The shown below is the first 91 data.

Column +1, +2, -1, -2 mean when patient was sunk in each condition, how much infusion dose should be used for reaching target 0.

Column +1 rule, +2 rule,-1 rule,-2 rule mean after changing fr by using the optimized rules shown above.

Column current +1rule, current +2rule, current -1rule, current -2rule mean after changing fr by using the hospital current rules.
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<td>1.33</td>
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</table>

Figure 2 Data compared with current practice
3.5 Test and Decision support system design

Test rules in simulation experiments, and especially test the rule for tolerance patients and sensitive patients. The results should be accepted. The new rules should need less time for finding the optimal dose for tolerance patient and sensitive patient.

Implement the decision support system by using optimized rules in Visual Basic 6.0. The decision table has been created. If and then rules could be used for establishing system. [12] Morning dose was calculated based on the earlier work. Follow the line: \[ MD = FR \times 97 + 40, \] we got the morning dose. [13]
4. Results

4.1 Calculation results

The infusion dose calculation results from each condition were shown as below:

X axis is displayed infusion dose might cause +2 +1 -1 -2 conditions

Y axis is difference

The plot in blue color is different between 0 and -1

The plot in brown color is different between 0 and -2

The plot in green color is different between 0 and +1

The plot with intersection is different between 0 and +2

Figure 4 graph for calculated difference between conditions and target 0
4.2 Bland-Altman plot

The data analysis includes finding difference and compare investigated rules with current practice rules. The results exist some data have exceed 1.96std. It seems that the data from database might have some noise. Get rid of noise influence.[15] The results are plotted by Bland-Altman plot method. Comparing investigated optimized rules with current rules, we find that investigated optimized rules more close to target 0, also the data in the +-1.96std interval. Correcting the errors though the plot picture, finally we get the whole titration rules.

The difference between the results and target 0 has been found. The results were displayed by Bland-Altman plot method. Consider a set of n samples. Both assays are performed on each sample, resulting in 2n data points. Each of the n samples is then represented on the graph by assigning the mean of the two measurements as the abscissa (x-axis) value, and the difference between the two values as the ordinate (y-axis) value. [9]

Hence, the Cartesian coordinates of a given sample S with values of S1 and S2 determined by the two assays is

$$S(x, y) = \left(\frac{S_1 + S_2}{2}, (S_1 - S_2)\right)$$

It is common to compute the limits of agreement during Bland-Altman analysis, which is the 95% confidence interval of the difference between the methods. This is defined as bias +/- 1.96 STD (average difference +/- 1.96 standard deviation of the difference). [10]

Showing as below:
Optimized rules

I. +1 condition

![Figure 5. +1 condition plots of optimized rules](image1)

Hospital current rules:

I. +1 condition

![Figure 6. +1 condition plots of current rules](image2)
II. +2 condition

Figure 7. +2 condition plots of optimized rules

Hospital current rules:

III. +2 condition

Figure 8. +2 condition plots of current rules
Optimized rules

IV. -1 condition

Figure 9. -1 condition plots of optimized rules

Hospital current rules:

V. -1 condition

Figure 10. -1 condition plots of current rules
Optimized rules

VI. -2 condition

[Graph showing optimized rules]

Hospital current rules:

VII. -2 condition

[Graph showing current rules]
After comparing results from optimized rules with current rules, the goodness can be easily seen in the shown picture above. Optimized rules make the data more round over zero than current rule does. That is mean the data organized by optimized rules can reach target zero more quickly than current rules. But some data have exceeded 1.96std. Redo the rules finding procedure, and fix the mini error in rules. At last we find the best titration rules for instead.

The titration rules can be described as below:

### 4.3 Titration rules

#### A. First step: Infusion dose Adjustments

- **< =1mg/min:**
  - Increase with 0.1 mg/min if you see Parkinsonism (-1) (-2)
  - Decrease with 0.1 mg/min if you see side effects (+1) (+2)
- **>1mg/min and <2mg/min:**
  - Increase with 0.1 mg/min if you see little Parkinsonism (-1)
  - Increase with 0.3 mg/min if you see more Parkinsonism (-2)
  - Decrease with 0.2 mg/min if you see side effects (+1)
  - Decrease with 0.2 mg/min if you see more side effects (+2)
- **>=2mg/min and <=3mg/min:**
  - Increase with 0.2 mg/min if you see little Parkinsonism (-1)
  - Increase with 0.4 mg/min if you see more Parkinsonism (-2)
  - Decrease with 0.3 mg/min if you see side effects (+1)
  - Decrease with 0.4 mg/min if you see more side effects (+2)
- **>3mg/min:**
Increase with 0.3 mg/min if you see little Parkinsonism (-1)

Increase with 0.5 mg/min if you see more Parkinsonism (-2)

Decrease with 0.4 mg/min if you see side effects (+1)

Decrease with 0.5 mg/min if you see more side effects (+2)

>4mg/min:

Increase with 2 mg/min if you see little Parkinsonism

Decrease with 1 mg/min if you see side effects

**B. Second step: Infusion dose fixing**

If you see the patient signs different effects after increasing (decreasing) infusion dose then the infusion dose should be decreased (increased) the dosage with 50%.[11]

For example:

The patient is treated by 2.1mg/min infusion dose and caused by little Parkinsonism (-1)

1 Dose is raised from 2.1mg/min to 2.3mg/min... (-1 rule driven: >=2mg/min and <=3mg/min: Increase with 0.2 mg/min if you see little Parkinsonism)

...making the patient hyperkinetic (+1).

2 Dose is lowered to 2.2mg/min...(Decrease dose with 50%, for the side effect hyperkinetic (+1)

...making the patient hyperkinetic (+1).

3 Dose is lowered to 2.15mg/min...

...leaving the patient normal (0).
5. Test

Firstly **random** one patient in simulation experiments

- ID 219 patient was chosen.

The X axis of TRS result is time in minutes and The Y axis is E value.

Set initial infusion dose 1.1mg/min.

1.1 mg/min -> 1.4 mg/min -> 1.7 mg/min -> 2 mg/min -> 2.4 mg/min

Five steps in total.

![Figure 13 test result of ID 219](image-url)
ID 308 patient was chosen.

The X axis of TRS result is time in minutes and The Y axis is E value.

Set initial infusion dose 1.1mg/min.

1.1 mg/min -> 0.9 mg/min -> 0.8 mg/min -> 0.7 mg/min -> 0.6 mg/min -> 0.5 mg/min -> 0.4 mg/min -> 0.45 mg/min  Eight steps in total.

Figure 14 test result of ID 308
ID 461 tolerant patient

Set initial infusion dose 1.1mg/min.

First day:

Give 1.1 mg/min -> 1.4 mg/min -> 1.7 mg/min -> 2 mg/min ->

2.4 mg/min -> 2.8 mg/min -> 3.2 mg/min -> 3.7 mg/min -> 4.2 mg/min

Figure 15 First day of ID 461
Second day:

Give 4.2 mg/min -> 6.2 mg/min -> 8.2 mg/min -> 10.2 mg/min (cause side effects) -> 9.2 mg/min -> 8.7 mg/min -> 8.5 mg/min

Figure 16 Second day of ID 461
ID 221 Sensitive Patient

Set initial infusion dose 1.1mg/min.

Give medicine every 120mins.

First day:

1.1 mg/min -> 0.9 mg/min -> 0.8 mg/min -> 0.7 mg/min ->

0.6 mg/min ->0.5 mg/min ->0.4 mg/min ->0.3 mg/min

Figure 17 First day of ID 221
Second day:

Change 0.3 mg/min -> 0.4 mg/min when the patient signs Parkinsonism.

The results show that new rules should be more quickly than current practice and less error when finding the optimal dose. The dose changing with new rules needs less days for finding the optimal dose and the new rules are suitable for tolerant and sensitive patients when testing in simulation experiments.
6. Conclusion

The final titration procedure rules were best among all the sets of rules. It is optimized by other rules when testing in simulation experiments. It combined all the situations in different conditions and resulted in rules. The final titration procedure rules reduced the number of steps for finding optimal dose. The error in finding optimal dose also has been decreased.

The titration rules maybe provides a convenient way for doctors and nurses for changing infusion dose when the effects come into view. In this research, the proper distance was found from each condition to optimal dose. A set of rules has been designed for levodopa infusion in PD disease based on simulation experiments. Meanwhile titration procedure rules are also invented. The procedure of new rules is more quickly and less error than current practice when finding the optimal dose. The tolerant and sensitive patients have been tested by the new rules. It has the same result as above: more quickly and less error than current practice. The results from testing the new patients randomly in simulation experiments were acceptable. With minimal overshoots and advantages in time and error, the new titration procedure rules should be compared with current practice rules in practice in the future.
7. Discussion

In this study of investigating a set of rules for dose adjustment, the infusion dose was changed by rules under the estimated E value, and too much morning dose or infusion dose might cause severe dyskinesias[14] However the effects are not adjusted by machine, only measured by doctors or nurses. There is not a specific boundary in between +1 and +2, -1 and -2. There would have some measuring errors in E value adjusting. The effects of patients might not been estimated when E value is between -0.5 and 0.5. Hence the E value has not been calculated by the simulation experiments in between -0.2 to +0.2.

With the purpose of minimal overshoots, the final titration procedure rules were invented. Based on the final titration procedure rules, the decision support system has been designed by using rule-based reasoning method. The rule-based reasoning for changing dose provides more detailed procedure of medicinal operations involving small changes. These rule-based advised changes step by step. When the effects come into view, the doctors or nurses can give the reasoning dose depend on the rules as soon as possible. The advantage of rule-based method is more safety and less error. These procedure rules were tested by the patients in simulation experiments. The results show that new rules have reduced the steps for finding the optimal dose and the time also have been decreased with the steps reduction. The extra dose utilizing in current practice would also be implemented in new rules. The purpose of using extra dose which has no influence to stable level is only for shorting time. This set of rules gave the acceptable results both in tolerant and sensitive patients’ simulation treatment. The morning dose was calculated via line: MD = FR * 97 + 40. It is depend on the earlier work of simulation experiments.[13]

Though all of exist unstable factors would probably affect to find optimal dose, the set of rules would give a reasonable way to reach the optimal infusion dose.
8. Future work

During this study, optimal morning dose depended on the earlier research. But during the simulation test, the morning dose sometimes makes a high E valve. It might cause side effects and always waste more time for finding optimal infusion dose. This difficult situation might be solved in future work.

Data selection during this study shortens the database, if we have all data in analyzing, the results should be more closely to target zero. These results would be improved in future work.
9. Acknowledgement

I am deeply grateful to Jerker Westin for his kindly instructions and for all his patience to answer all my doubts and questions.

Special thanks go to my partner Jian Wang for his earlier research contributions

Finally, I would like to thank my family for their support and encouragement and my friends those who helped me during the processing of writing this thesis.
Reference


Appendix I Code for calculating FR in +2 condition

global $BASE;
global $EMAX;
global $EC50;
global $gamma;

global $Inf;
global $SMD;
global $FR;

global $ka;
global $k12;
global $k21;
global $BIO;
global $ke;
global $Rsyn;
global $keo;
global $v1;
global $v2;

$time = 3000 + 1;

include_once ('Connt.inc.php');
include_once ('./runge4.php');;
mysql_select_db ( 'pkpdduodopa' );

$string = "select * from du_patient_general where du_emax+du_base>=2";
$result = mysql_query ( $string );
$num = mysql_num_rows($result);

set_time_limit(0);
$file = fopen('file1.txt','w');
while ( $row = mysql_fetch_row ( $result ) )
{
   $id = $row [0];
   $tabs = $row [1];
   $ka = 1 / $tabs;
   $stkeo = $row [2];
   $keo = 1 / $stkeo;
   $BIO = $row [3];
   $v1 = $row [4];
   $v2 = $row [5];

   $cl = $row [6];
   $ke = $cl / $v1;

   $q = $row [7];
$k12 = \frac{q}{v1};$
$k21 = \frac{q}{v2};$

$Rsyn = \text{row}[8];$
$EMAX = \text{row}[9];$
$BASE = \text{row}[10];$
$EC50 = \text{row}[11];$
$gamma = \text{row}[12];$

$Inf = \text{row}[13];$
$stop = false;$
$\text{$Inf = Inf + 0.01;}$

fputs($file,"\n");
fputs($file,$id.' ');
$\text{Temp = 10000;}$
while(!$stop)
{
    $arr = \text{array (0, 0, 0, 0 );}$
    $val = \text{runge4 } ( \text{$arr, 1, \text{time, total, half_temp, full});}$
    $average = 0;$
    for($i = 0; $i < 10; $i ++) {
        $average = $average + $val [sizeof($val) - 1 - i];
    }
    $average = $average / 10;
    $average = $average - 2;
    if(abs($average)>$templabs($average)<=0.2) {
        $stop=true;
    }
    else {
        $Inf = $Inf + 0.01;
        $temp = abs($average);
    }
}

fputs($file,$Inf);

fclose($file);
echo 'calculation is done!';
echo '<br/>';
Appendix II Code for decision support system

Private Sub Command1_Click()
Dim a As Single
Dim b As Single
Dim c As Single
Dim d As Single

a = Text1.Text
b = Text2.Text

If a > 1 And a <= 2 And b >= 0 And b <= 1 Then c = b - 0.1
If a > 1 And a <= 2 And b > 1 And b < 2 Then c = b - 0.3
    If a > 1 And a <= 2 And b >= 2 And b < 3 Then c = b - 0.4
        If a > 1 And a <= 2 And b > 3 Then c = b - 0.5

If a > 0 And a <= 1 And b >= 0 And b <= 1 Then c = b - 0.1
If a > 0 And a <= 1 And b > 1 And b < 2 Then c = b - 0.2
    If a > 0 And a <= 1 And b >= 2 And b <= 3 Then c = b - 0.3
        If a > 0 And a <= 1 And b > 3 Then c = b - 0.4

If a >= -1 And a < 0 And b >= 0 And b < 2 Then c = b + 0.1
    If a >= -1 And a < 0 And b >= 0 And b >= 2 And b <= 3 Then c = b + 0.2
        If a >= -1 And a < 0 And b >= 2 And b <= 3 Then c = b + 0.3

If a >= -2 And a < -1 And b >= 0 And b < 1 Then c = b + 0.1
    If a >= -2 And a < -1 And b >= 1 And b < 2 Then c = b + 0.3
        If a >= -2 And a < -1 And b >= 2 And b <= 3 Then c = b + 0.4
            If a >= -2 And a < -1 And b > 3 Then c = b + 0.5

If a = 0 Then c = b

d = c * 97 + 40

Text3.Text = c
Text4.Text = d

End Sub