Determine the Optimal Dose of Atorvastatin
by AHP and Multi-Criteria Game Theory

Ensiyeh Doosthoseini
Department of Mathematics, Shahed University, Tehran, Iran
hosseini_86@yahoo.com

Hamidreza Navidi
Department of Mathematics, Shahed University, Tehran, Iran
navidi@shahed.ac.ir

Majid Hassanpour-ezatti
Department of Biology, Shahed University, Tehran, Iran
hassanpour@shahed.ac.ir

Abstract
Nowadays, Multi Attribute Game Theory model helped to physicians in situation of uncertainty medical decision making for prescribing of drugs. Narrowing of coronary heart and reduction in heart blood flow are important cause of coronary heart disease (CHD). Control of blood lipid level is routine treatment in CHD patients. But damage to liver and cardiac muscles are common sides effect of lipid lowering drug medication. Measurement of plasma ALT and CPK levels considered as markers of liver and cardiac muscles damage respectively. In this study, Multi Attribute Game Theory based drug dose determination used for prescription of Atorvastatin dose as a lipid lowering drug patients. Here, optimum dose defined as a dose that decreases plasma LDL with low side effects. In our model, decrease in LDL consider as positive consequences and increase in plasma ALT and CPK as side effect of this drug. This method offer 80 mg/day as an optimum dose which is also corresponds with some medical magazine articles. This result showed that quality of this models output is near to clinically approved decision. Thus this model can be considered as an applicable decision making model for physician and pharmaceutical industries about dosing of this drug in a similar situation.

Keywords: Multi Attribute Game Theory, CHD patient, dosage, Atorvastatin
1 Introduction

Nowadays, application of mathematical systems in medical sciences is an ever-growing field, particularly in medical decision-making. Game Theory, fuzzy systems, neural networks have been presented to help the physician improve or optimize diagnostic and therapeutic procedures. Coronary artery disease is one of the most important causes of mortality in human societies throughout the world. Occlusion of coronary arteries (which is caused by multiple factors) results in myocardium (the heart musculature) not receiving enough blood flow. Increased LDL is among important sign of coronary heart disease and are associated with increased probability of heart attack. Daily use of LDL-reducing drugs helps preserve the coronary arteries from occlusion [1]. Among these drugs, one family known as Atorvastatins receive a big share of the market due to their efficient LDL decreasing properties [2]. One well-known adverse reaction of these drugs, however, is elevated plasma levels of the hepatic enzyme Alanine Aminotransferase (ALT, formerly known as SGPT). Under normal conditions, this enzyme inside liver cells; however, in case of liver injury, the damaged liver cells release this enzyme into the blood stream, thus elevating its serum level [3]. An elevated level of this enzyme indicates liver damage which may be caused by inappropriate dosage of Atorvastatin. Cardiac muscle injury called Myopathy is another side effect caused incorrect dose taking. Increasing levels of CPK in blood is a symptom for Myopathy[4].

In medical practice, different doses of Atorvastatin (10, 20, 40 and 80 mg/day) are prescribed to patients. Our goal is to determine that dose of Atorvastatin which decreases LDL in CHD patients efficiently while causing side effects minimally. In this paper, we use a mathematical model to determine the optimum dose based on Game theory logic system with minimal liver and Cardiac muscle injury.

The goal of this research is the comparison among different doses of Atorvastation from cholesterol reduction point of view with respect to its side effects for the patients with narrowed coronary artery disease. In this project we estimate the optimal dose using two AHP and multi criteria game Theory. By optimal dose we mean the dose with highest reduction in LDL but less side effects, among the four doses.

2 Methodologies

By optimum dose we mean that dose of Atorvastatine with most LDL reduction and least side effects. The tool should have the capability to select the optimum dose for most LDL reduction and least in ALT and CPK indicators, from one side, and the capability for competitive modeling between disease as a player which its aim is to increase cholesterol and relevant side effects against drug Theory by physician for decreasing cholesterol side effects, from other side. To achieve such a goal, we utilize a new Theory called multicriteria game Theory. This new Theory utilizes both Game Theory and multicriteria decision making Theory.
Simultaneously.
The required data extracted from pumbed site and among the articles published between 1990 to 2010 regarding the patients with narrowed coronary artery and up taking A
torvastation with the dose under investigation in this research. In fact, there are two intelligent and no intelligent players as physician and disease, for our model, respectively. The strategy taken by the physician is to modify doses such that least side effects and most cholesterol reduction achieved [5].

Physician strategy:

\[ O_1 = \{ \text{Dose 10mg/day = A, dose 20mg/day = B, dose 40mg/day = C, dose 80mg/day = D} \} \]

Disease strategy:

Disease is a no intelligent player against the intelligent physician. The strategy of the disease is no respond to Atorvastain suitably. Therefore, the aim of the disease is to increase cholesterol sediments and narrowing the coronary artery. Furthermore the exact strategy of the disease is not clear to the physician [5].

\[ O_2 = \{ \text{Dose10mg/day = A', dose20mg/day = B', dose 40mg/day = C', dose 80mg/day = D'} \} \]

The steps of approaching to the problem solution are as follows: At the first step computation should run from physician point of view. At this step the AHP graphs for all possible combinations of the physician and disease strategies regarding [6]. LDL, ALT and CPK criteria should be building up. The next step is to construct the decision making matrices for all AHP graphs and computation of relative weight for all of the decision matrices. At last the final weight of all strategies taken by the physician, compute. All the above steps carry on once again from disease point of view. Finally reward matrix of the players builds up and the game equilibrium using Game Theory, achieves. At the first step the graph of AHP related to the game between physician and disease drawn

Fig 1: the graph of AHP for physician and disease game

There are 16 combinations of total strategies between physician and disease. In each step for solving the problem, 16 possible graphs of AHP should be built up. Step one: This step is followed by physician. The priorities of the criteria are as follow
The decision making matrices extracted from AHP graph are as follows:

\[
\begin{pmatrix}
1 & 9 & 9/2 \\
1/9 & 1 & 1/2 \\
2/9 & 2 & 1 \\
\end{pmatrix}
\]

The decision making matrices of AHP related to the combination of strategies with respect to LDL, ALT, and CPK criteria, from physician point of view as follows:

\[
\begin{pmatrix}
A & B' \\
A' & B \\
\end{pmatrix}
\]

\[
\begin{pmatrix}
1 & 9/8 \\
8/9 & 1 \\
\end{pmatrix}
\]

\[
\begin{pmatrix}
1 & 4/3 \\
3/4 & 1 \\
\end{pmatrix}
\]

\[
\begin{pmatrix}
1 & 1/5 \\
5 & 1 \\
\end{pmatrix}
\]

The next step is to compute weight of physician strategies with respect to all AHP graphs. To extract the weight of physician strategy, the eigenvector method is used.

\[
W_{A}(LDL) (A, A') = 0.5 \\
W_{C}(LDL) (C, A') = 0.87
\]

The reward matrix of the physician is as below:

\[
\begin{pmatrix}
A & B' & C & D' \\
A & 0.5 & 0.734168 & 0.6949 & 0.691663 \\
B & 0.2558 & 0.5 & 0.485824 & 0.501079 \\
C & 0.295008 & 0.504176 & 0.5 & 0.508339 \\
D & 0.29917 & 0.4971 & 0.4833 & 0.5 \\
\end{pmatrix}
\]

Step two: This step is from disease point of view. The aim of disease unlike the physician is increasing cholesterol. The strategies are different doses of station as mentioned before.

The priorities from disease point of view for LDL are complementary of the priorities from physician point of view [7].

The priorities disease point of view for ALT is directly related to the priorities physician point of view [8].

The priorities from disease point of view for CPK are inversely related to the priorities from physician point of view [8].
Determine the optimal dose of Atorvastatin

<table>
<thead>
<tr>
<th>CPK</th>
<th>ALT</th>
<th>LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/9</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>1/8</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2: Priority of each Atorvastatin dose used from physician point of view and the prevalence of using this dose to each criteria

The decision making matrices of the AHP graphs are as follows:

\[
\begin{bmatrix}
  LD & ALT & CPK \\
  LD & 1 & 9 & 9/2 \\
  ALT & 1/9 & 1 & 1/2 \\
  CPK & 2/9 & 2 & 1 \\
\end{bmatrix}
\]

The decision making matrices of the AHP graph related to the combination of strategies with respect to LDL, ALT and CPK criteria from disease point of view are as follows:

\[
\begin{bmatrix}
  A' & B \\
  A' & 1 & 8/7 \\
  B & 7/8 & 1 \\
\end{bmatrix}
\]

From disease point of view:

\[ W_d(LDL)(A', A) = 0.5 \]
\[ W_c(LDL)(C, A) = 0.38 \]

The disease reward matrix is as below:

\[
\begin{bmatrix}
  A' & B' & C' & D' \\
  A & 0.5 & 0.488329 & 0.497507 & 0.29917 \\
  B & 0.506588 & 0.5 & 0.467524 & 0.291674 \\
  C & 0.492495 & 0.485824 & 0.5 & 0.25831 \\
  D & 0.691663 & 0.698326 & 0.740836 & 0.5 \\
\end{bmatrix}
\]

Having reward matrices and by help of Game Theory we can obtain the equilibrium point of the Game. To do this required ranking of the reward matrices. It is assumed that physician plays in row and disease plays in column. Therefore the physician reward matrix should be ranked in row. These matrices are as follows:

\[
R^\text{Physician} = \begin{bmatrix}
4 & 4 & 4 & 4 \\
1 & 2 & 2 & 2 \\
2 & 3 & 3 & 3 \\
3 & 1 & 1 & 1 \\
\end{bmatrix}
\]

\[
R^\text{Disease} = \begin{bmatrix}
2 & 3 & 1 & 4 \\
2 & 3 & 1 & 4 \\
2 & 1 & 3 & 4 \\
3 & 2 & 1 & 4 \\
\end{bmatrix}
\]

Having the above matrices and by help of game theory we could recognize that the combination of the strategies \((10, 80 \text{ mg/day})\) leads to the optimum game equilibrium point.
3 Conclusions

The above data show that the combination of the strategies of the different doses in this article leads to the optimum game equilibrium by selection of (10, 80 mg) doses. Hence, the physician as a first player with the goal of most reduction of cholesterol and least side effect selects the dose 80 mg/day as an optimum dose. In the other hand, disease as a second player and as a physician competitor with the goal of least respond to drug, selects the dose 10 mg/day as an optimum dose. Regarding the point that reportedly patients using Atorvastatin rarely involved liver damages and Myopathy, Therefore the physician could select a dose with highest cholesterol reduction power without any main concern about severe side effects. But the goal of the disease is maintaining the undesirable condition by the dose with least power of cholesterol reduction.

References


Received: December, 2010