Comparison of AHP and Game Theory Methods to Determine Optimal Dose of Atorvastatin in CHD Patients

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Abstract

CHD are a result of the narrowing of the coronary arteries. Measuring the LDL level of the blood is an important way of diagnosing and treating the disease. Atorvastatin decreases the blood’s LDL level through cholesterol inhibition. Doctors can prescribe different doses of the drug as a player against the disease in a doctor-patient setting modeled as a game. The drug may damage liver and the heart muscle as a side effect which are measured through the blood level of the enzymes ALT and CPK. We have prescribed the appropriate dosage of the drug using the information collected for the Pubmed publications and through AHP and multi-criteria game theory in this research. These methods offer 80 mg/day as an optimum dose which is also corresponds with some medical magazine articles. This result showed that quality of this Multi Attribute Game Theory and AHP models output is near to clinically approved decision. Thus this models 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, AHP, CHD patients, dosage.

1 Introduction

Nowadays, application of mathematical systems in medical sciences is an ever-growing field, particularly in medical decision-making. Game Theory, AHP, fuzzy systems, neural networks, and expert systems 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[1]. 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 is associated with increased probability of heart attack [1]. Daily use of LDL-reducing drugs helps preserve the coronary arteries from occlusion. 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 ALT. 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. An elevated level of this enzyme indicates liver damage which may be caused by inappropriate dosage of Atorvastatin [3]. 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 two mathematical models to determine the optimum dose based on Game theory and AHP with minimal liver and Cardiac muscle injury. Since there is no general formula for drug administration, this implementation of Game theory can be of considerable aid to doctors to figure out the optimal dose with a minimum of side effects. 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 methods. By optimal dose we mean the dose with highest reduction in LDL but less side effects, among the four doses.

2 Methodologies

- AHP
One of the effective techniques is AHP first introduced by Thomas L.saaty [5]. This technique is based on pair-wise comparison and yields different scenarios.
The methodology of solving the problem is as follows:

1. creating Hierarchies
2. priority computing
3. System consistency

The first step in AHP is to create a graphical representation of the problem showing the target, criteria, and options. The following graph shows the optimum dose selection by AHP. As shown in graph 1, the level one in AHP shows the optimum dosage and level two shows three criteria namely LDL, ALT, CPK and the third level gives the four different dose options for Atorvastatin.

![Graph 1: Optimum dose selection by AHP](image)

The second step is to compute the priorities. In AHP method the elements of each level is compared to the next level as pair-wise comparison and their priority computed, which is called local priority. Then composing the local weighs gives the final priority of each option, called overall priority. The doses compared regarding their ability to reduce LDL percent and to increase ALT and CPK percents separately and identifying their priority with respect to those criteria then the priority of criteria with respect to the target is determined and by their combination the overall priority of the doses identified. We should mention that all of the comparisons is AHP carried on as pair-wise comparison.

For example if we suppose to compare doses regarding the percentage of reduction in LDL, we should first compare the doses of A with respect to B and then continue this comparisons for A with C and A with D and B with C and B with D and D with C. Also the physicians use their judgment for comparison, which is converted into quantitative between 1 to 9 and shown in the following table.

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

**Table 1. The preference of each doses used in Atorvastatin**

Local priority of different doses of Atorvastatin measurements Note that in the pair-wise comparison, the preference of each element with respect to itself is one,
hence all elements on the diagonal of pair-wise comparison matrix are one. Also if the dose 20 (mg/day) with respect to dose 10 has the preference of 5, then dose 10 (mg/day) with respect to dose 20 has the preference of 1/5, in this case the pair-wise comparison matrix becomes as below:

\[
\begin{pmatrix}
A & B & C & D \\
A & 1 & 1/5 & 1/7 & 1/8 \\
B & 5 & 1 & 5/7 & 5/8 \\
C & 7 & 7/5 & 1 & 7/8 \\
D & 8 & 8/5 & 8/7 & 1
\end{pmatrix}
\]

Pair-wise comparison matrix for four different Atorvastatin doses regarding ability to reduce LDL.

When the pair-wise comparison matrix was formed, then we could compute the priority of each dose. In other words, using pair-wise comparisons introduced in the pair-wise comparison matrix, the priority of each dose with respect to percentage reduction in LDL, can be identified. To compute the priority of each dose from pair-wise comparison matrix, the local priority, the method of Eigen vector has been used. The priority vectors which show the local priority of the doses A, B, C, D. Regarding the percentage of increase in ALT criteria, are as follows:

\[
\lambda = 4 \quad (0.047, 0.237, 0.333, 0.382)
\]

\[
\begin{pmatrix}
A & B & C & D \\
A & 1 & 4/3 & 4/2 & 4 \\
B & 3/4 & 1 & 3/2 & 3 \\
C & 2/4 & 2/3 & 1 & 2 \\
D & 1/4 & 1/3 & 1/2 & 1
\end{pmatrix}
\]

Pair-wise comparison matrix for four different Atorvastatin doses regarding ability to reduce ATL.

\[
\lambda = 4 \quad (0.4, 0.3, 0.2, 0.1)
\]

\[
\begin{pmatrix}
A & B & C & D \\
A & 9/8 & 9 & 9 \\
B & 8/9 & 1 & 8 & 8 \\
C & 1/9 & 1/8 & 1 & 1 \\
D & 1/9 & 1/8 & 1 & 1
\end{pmatrix}
\]

Pair-wise comparison matrix for four different doses of Atorvastatin regarding the CPK increase.

The priority vector which show the local priority of the doses A, B, C, and D, regarding the percent of increase in CPK criteria, are as follows:

\[
\lambda = 4 \quad (0.4737, 0.4210, 0.05, 0.05)
\]

It should be pointed out that the positive \( \lambda \) means consistency of the interpretation in the decision making matrices. After computing the priority of doses with respect to all criteria, the priority of criteria should also be identified, in other words the contribution of each criteria in determining the best dosage should be identified.
Comparison of AHP and game theory methods

To do this it is required to compare the criteria as well. The pair-wise comparison matrix of the criteria has been shown in the following table:

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

Using eigenvectors yield the priority of criteria as follow:

\[
\text{LDL} \quad 0.75, \quad \text{ALT} \quad 0.0833, \quad \text{CPK} \quad 0.166
\]

As seen above, the priority of LDL criteria is the most.

The overall priority of each doses can be determined by the sum of the products of the priority of each criteria times the priority of its doses. The following table shows the priority of the doses with respect to the criteria.

<table>
<thead>
<tr>
<th></th>
<th>LDL</th>
<th>ALT</th>
<th>CPK</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.047</td>
<td>0.4</td>
<td>0.4737</td>
</tr>
<tr>
<td>B</td>
<td>0.2883</td>
<td>0.3</td>
<td>0.4210</td>
</tr>
<tr>
<td>C</td>
<td>0.332</td>
<td>0.2</td>
<td>0.05</td>
</tr>
<tr>
<td>D</td>
<td>0.382</td>
<td>0.1</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Table 2. Determining the overall preference of the different doses of Atorvastatin

The overall priority of each dose regard to the local priorities can be determined as follow:

-The overall priority of dose A: \(0.75 \times 0.047 + 0.0833 \times 0.4 + 0.166 \times 0.4737 = 0.1467\)
-The overall priority of dose B: \(0.75 \times 0.238 + 0.0833 \times 0.3 + 0.166 \times 0.4210 = 0.2735\)
-The overall priority of dose C: \(0.75 \times 0.232 + 0.0833 \times 0.2 + 0.166 \times 0.05 = 0.2724\)
-The overall priority of dose D: \(0.75 \times 0.382 + 0.0833 \times 0.1 + 0.166 \times 0.05 = 0.3016\)

The preference of the different doses of Atorvastatin regarding their computed priorities is as follow:

<table>
<thead>
<tr>
<th>priority</th>
<th>dose</th>
<th>rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1467</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>0.2735</td>
<td>B</td>
<td>3</td>
</tr>
<tr>
<td>0.2724</td>
<td>C</td>
<td>2</td>
</tr>
<tr>
<td>0.3016</td>
<td>D</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 3. Determining the preference of the different doses of Atorvastatin

- Multi Attribute Game Theory

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 multi-criteria game Theory. This new Theory utilizes both Game Theory and multi-criteria decision making Theory Simultaneously [6].

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.

**Physician strategy:**

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

**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.

\[ O_2 = \{ \text{Dose 10 mg/day} = A', \text{dose 20 mg/day} = B', \text{dose 40 mg/day} = C', \text{dose 80 mg/day} = D' \} \]

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. 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 2: the graph of AHP for physician and disease game](image)
There are $4 \times 4$ combinations of total strategies between physician and disease.

One step is followed by physician. The priorities of the criteria are as follows:

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

*Table 4.* Priorities from physician point of view

$$
\begin{bmatrix}
LDL & Alt & Cpk \\
LDL & 1 & 9 & 9/2 \\
Alt & 1/9 & 1 & 1/2 \\
Cpk & 2/9 & 2 & 1
\end{bmatrix}
$$

The reward matrix of the physician is as below:

<table>
<thead>
<tr>
<th>$A'$</th>
<th>$B'$</th>
<th>$C'$</th>
<th>$D'$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$</td>
<td>0/5</td>
<td>0/734168</td>
<td>0/6949</td>
</tr>
<tr>
<td>$B$</td>
<td>0/2558</td>
<td>0/5</td>
<td>0/485824</td>
</tr>
<tr>
<td>$C$</td>
<td>0/295008</td>
<td>0/504176</td>
<td>0/5</td>
</tr>
<tr>
<td>$D$</td>
<td>0/29917</td>
<td>0/4971</td>
<td>0/4833</td>
</tr>
</tbody>
</table>

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].

<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 5.* Priority of each Atorvastatin dose used from disease point of view

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 matrixes. It is assumed that physician plays in row and disease plays in column. Therefore the physician reward matrix should be ranked in row [6]. These matrices are as follows:

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

Having the above matrices and by help of game theory we could recognize that the combination of the strategies (10, 80) 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 10 and 80 mg/day as an optimum doses. 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. More over using AHP method offers that 80 mg dose is the best suggestion to the physician and hence two methods converges to one result.

References


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