Analysis of physicochemical properties of drugs included in anticholinergic rating scales

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Abstract

Adverse effects induced by the duplication of drugs with anticholinergic effects are a problem among elderly people who take many drugs. Various anticholinergic rating scales have been published and are applied clinically to evaluate a patient’s anticholinergic burden; however, there are some problems with these scales, such as drugs that are assessed differently between scales. We aimed to construct a method to more correctly distinguish between drugs with and without anticholinergic effects and to understand the properties of drugs that have anticholinergic effects. We constructed a model for identifying anticholinergic effects via a decision tree, using descriptors indicating the physicochemical properties of the drugs. The best split yielded a decision tree with 46 branches (area under the receiver operating characteristic curve = 0.99). However, only seven branches, defined by six descriptors: ASA_P, GCUT_PEOE_0, opr_brigid, PEOE_VSA+1, GCUT_SLOGP_0, vsa_pol (related to van der Waals surface areas, partial charges, and molecule structures), were required to identify drugs with anticholinergic effects. This result suggests a relationship between the hydrophobic interactions of drugs and the muscarinic receptor. In this study, we constructed a model to predict whether drugs have anticholinergic effects, and obtained essential physicochemical information on the drugs to distinguish their anticholinergic effects. It is our hope that these findings provide useful information for predicting anticholinergic effects of drugs in clinical settings.

Key Words: anticholinergic rating scales, adverse effects, polypharmacy, Structure-Activity Relationship, decision tree

Area of Interest: Information and computing approach for drug design and ADMET study
1. Introduction

Polypharmacy in elderly people is an increasing phenomenon in developed countries with aging populations. This has led to problems such as adverse effects caused by duplication of anticholinergics and drug interactions related to cytochrome P450 [1]. Psychotropics, antihistamines and therapeutic agents for overactive bladders are typical anticholinergics that are widely prescribed to elderly people.

Anticholinergic side effects include well-known anti-muscarinic effects: dry mouth, tachycardia, constipation, and urinary hesitancy [2]. Additionally, falls and cognitive impairment are side effects that require special caution, because these have a negative effect on healthy life expectancy.

Several anticholinergic rating scales have been published which provide information on drugs, including the presence or absence and strength of anticholinergic effects. Drugs that are not muscarinic receptor antagonists are also included as anticholinergics on these scales. Most anticholinergic rating scales are constructed using expert opinions based on a close examination of the literature, and the evaluation of the strength of anticholinergic effects are different among these scales [3]. Experimental data on anticholinergic effects have also been used for some scales, but these data are pointed out of limitation; the anticholinergic activity assay is not considered administered dosage and active metabolites [4]. Furthermore, anticholinergic rating scales do not cover all approved drugs at present, despite the fact that it is necessary to check the anticholinergic effects of each drug prescribed to a patient in order to correctly evaluate the patient’s anticholinergic burden. For these reasons, one goal of this study is to integrate the differences between various anticholinergic rating scales and construct a method for predicting the anticholinergic effects of drugs that do not appear on the scales.

The binding of drugs to a target region causes an internal pharmacological effect, followed by absorption and distribution after administration. These interactions depend on the physicochemical properties of each drug, such as lipophilicity, polarity and three-dimensional structure. The properties characterizing each drug can be described as values calculated from a chemical structural formula, called a ‘descriptor’. Analysis of the relationship between descriptors and bioactivity is based on an approach to structure-activity relationships that can be summarised as ‘similar structures have a similar activity’. This approach has been used to explore lead compounds and predict pharmacokinetics and toxicities in drug discovery [5].

We considered that additional information based on physicochemical properties—that is, the specific characteristics of each drug—might contribute to overcoming the problems associated with anticholinergic rating scales. If a prediction model of anticholinergic effects, based on descriptors, could be constructed, it could be applied to drugs whose anticholinergic effects have not yet been evaluated.

A decision tree is a decision-support tool that is constructed using data. Its results are easier to understand than those of other such methods, such as discriminant analysis, logistic regression, and machine-learning approaches [6].

2. Methods

2.1 Drugs used in the decision tree, and their anticholinergic effects
We obtained data on drugs published in anticholinergic rating scales from seven articles [7-13] used in a systematic review [3] that evaluated the differences between each anticholinergic rating scale and the relation between anticholinergic burden and adverse effects. In these articles, drugs were ranked by the strength of their anticholinergic effects. We wished to distinguish between drugs based on the presence or absence of anticholinergic effects, so we searched for drugs with or without anticholinergic effects, regardless of the strength of those effects. Even if the reported effects of a drug differed among articles, we concluded that it had anticholinergic effects if it was reported as such in at least one article. We excluded drugs that were duplicated or drugs for which we were unable to calculate descriptors.

### 2.2 Calculation of descriptors

We obtained the drug structure data described in section 4.1 from Drugbank (version 5.0.3) [14]. When the drug structure data were not present in Drugbank, we obtained them from PubChem [15] or KEGG [16]. We calculated descriptors from these structure data using the integrated computational chemistry system Molecular Operating Environment (MOE) 2015.1001 (Chemical Computing Group Inc., Montreal, Quebec, Canada). First, water molecule and counter ions were eliminated from the structure data of each drug by processing of disposal salts. Next, the structure data, after an energy minimisation calculation, were changed to a 3D form using 'Rebuild 3D', and assigned partial charges with 'Partial Charges'. After preparing the data in this manner, we excluded duplicate drugs, and calculated the descriptors using MOE. We calculated all 2D and 3D descriptors, but descriptors classified as proteins were excluded.

### 2.3 Construction of a discriminant model using a decision tree

We produced a decision tree for the presence or absence of anticholinergic effects using the descriptors obtained as described in section 4.2 as explanatory variables. We used the software JMP Pro 12.2.0 (SAS Institute Inc., Cary, NC, USA) to construct the decision tree. In the branch algorithm in this software, a tree is split to maximise the branch statistic value of the likelihood ratio chi-square [17]. We validated the model with K-fold cross-validation. K-fold cross-validation is a method for calculating cross-validation statistics. In this method, all data are randomly partitioned into K subsets, called folds. Each fold contains the same amount of data and is independent of the others. Each fold is treated as a holdback sample while the remaining observations are used as a training dataset. The method then estimates the model parameter for K−1 groups and validates the error using the remaining group. These processes are repeated a total of K times [18]; we set K = 5. The decision tree is repeatedly split until the improvement in the cross-validation R² resulting from an additional split is minimal.

### 3. Results

#### 3.1 Drugs and descriptors

In total, we obtained 545 drugs from seven articles [7-13]. Bismuth subsalicylate was excluded due to the many missing values in its calculated descriptors. We included 174 drugs that had anticholinergic effects and 371 without anticholinergic effects. These drugs were used to construct a decision tree.

The drugs are shown in Tables 1 and 2. Table 1 shows drugs that have anticholinergic effects,
together with their node number in the decision tree. Table 2 shows drugs that do not have anticholinergic effects. After excluding descriptors with missing values from the initial 354 descriptors calculated, we used 336 descriptors to construct the decision tree.

Table 1. Drugs that have anticholinergic effects

| Node | Anticholinergic effect |
|------|-----------------------|
| 1    | thalidomide           |
| 2    | mepipramine           |
| 3    | amitriptyline         |
| 4    | doxepine              |
| 5    | loxapine              |
| 6    | loxapine              |
| 7    | loxapine              |

Table 2. Drugs that do not have anticholinergic effects
3.2 Decision tree

The best split, using five-fold cross-validation, yielded a decision tree that branched 46 times. However, we found that a decision tree that with seven branches was sufficient to capture the most important descriptors relating to anticholinergic effects, since this was the lowest number of branches for which the area under the receiver operating characteristic (ROC) curve (AUC) was over 0.8 ($R^2 = 0.258$, AUC = 0.816). Figure 1 shows the changes in $R^2$ with the number of branches. Figure 2a shows the ROC curve and AUC for the best split, and Figure 2b shows the same for the seven-branch tree. Figure 3 shows the seven-branch decision tree, including its leaf node numbers.

More than 50% of the drugs in leaf nodes 3, 7 and 8 of the seven-branch tree have anticholinergic effects. These nodes included antidepressants, benzodiazepines and antipsychotics. In addition, antimuscarinics, including atropine, were found in all three of these nodes, as well as in node 5.

The conditions for branching that led to node 8, which included the highest proportion of drugs with anticholinergic effects, were $ASA_P$ (a 3D descriptor representing the water-accessible surface area of all polar atoms) < 96.5 and $GCUT_{PEOE}_0$ (a GCUT descriptor calculated by allocating partial charges to atoms. The GCUT descriptors are calculated from the eigenvalues of a modified graph distance adjacency matrix.) < −0.859. Node 7 had the second-highest proportion of anticholinergics, and its conditions were $ASA_P < 96.5$, $GCUT_{PEOE}_0 ≥ −0.859$, $opr_{brigid}$ (the number of rigid bonds defined in Oprea [19]) ≥ 17 and $PEOE_{VSA}+1$ (a descriptor calculated from the sum of van der Waals surface areas of atoms with partial charges) < 87.7 (Figure 3).

Although the first branch condition leading to node 3 was $ASA_P ≥ 96.5$ (in contrast to that for nodes 7 and 8), the subsequent branch conditions were $GCUT_{SLOGP}_0$ (a descriptor related to SlogP that is estimated value of the octanol-water partition coefficient (log $P$). $< 0.034$ and $vsa_{pol}$ (an approximation of the sum of van der Waals surface areas of polar atoms) $< 27.4$. The proportion of drugs in node 3 that are anticholinergic was 52.4%, the third-highest in the tree.

Branch conditions leading to the nodes for which the proportion of anticholinergics was $≥ 50\%$ thus featured the following six descriptors: $ASA_P$, $GCUT_{PEOE}_0$, $opr_{brigid}$, $PEOE_{VSA}+1$, $GCUT_{SLOGP}_0$ and $vsa_{pol}$. These important descriptors for distinguishing the anticholinergic effects of drugs are related to van der Waals surface areas, partial charges, hydrophobicity, and three-dimensional structures [20].

The predicted performance of the model, based on the best branch, was $R^2 = 0.681$ and AUC = 0.990.

![Figure 1](image_url)

**Figure 1.** $R^2$ with increasing number of decision tree branches, up to the best-split tree, which branched 46 times
Figure 2. a. ROC curve and area under the ROC curve (AUC) for the best-split decision tree, according to five-fold cross-validation. b. ROC curve and AUC for the seven-branch decision tree, according to five-fold cross-validation. The horizontal axis is 1-specificity, the longitudinal axis is sensitivity. AUC is used for evaluating predict performance of model. As AUC is larger value (as ROC curve is closer to the left upper), prediction performance is better.

Figure 3. The seven-branch decision tree, produced using five-fold cross-validation. The text at the top of each node indicates the condition under which that node would be selected. The horizontal bar graphs in each node indicate the number of drugs that have anticholinergic effects (white) and of those that do not (grey). The terminal leaf nodes are numbered 1 to 8. The percentage next to the leaf node number indicates the proportion of anticholinergics in each node.

4. Discussion

A discriminant model was constructed from a decision tree, using calculated descriptors based on drugs appearing in anticholinergic rating scales. The three nodes (3, 7, 8) that had > 50% anti-
cholinergics in the seven-branch tree included drugs with known anticholinergic effects (antimuscarinics, antidepressants and antipsychotics) recorded in Goodman and Gilman’s The Pharmacological Basis of Therapeutics [21]. According to these results, we conclude that even with a small number of branches, a decision tree can distinguish anticholinergic drugs to some extent.

The essential descriptors, which were related to the drugs’ physicochemical properties, that were identified by the seven-branch model are known to relate to the strength of hydrophobicity and conformational changes in chemical compounds. The structure of the muscarinic receptor antagonist is known to be a pharmacophore: a hydrophobic group interacts outside of the acetylcholine-binding site, an ester forms a hydrogen bond, and a nitrogen atom with a positive charge creates ionic interactions with each amino acid residue at the acetylcholine-binding site [22]. Antagonists generally have a small structural similarity to an endogenous ligand, and have an additional hydrophobic group compared to agonists. They also have a higher affinity to the receptor than agonists, because the hydrophobic site interacts with the receptor through van der Waals forces and hydrophobic effects [23]. Our results therefore suggest that anticholinergic effects are caused by hydrophobic interactions between the muscarinic receptor and the physicochemical properties of drugs that meet the conditions for descriptors appearing in this discriminant model.

In node 2, the proportion of anticholinergic drugs was small (21.5%), but the actual number of anticholinergic drugs was relatively large (59). This node included disopyramide, which is known to cause anticholinergic side effects by acting on the muscarinic receptor [24], as well as drugs that are generally placed in pharmacological classes other than antimuscarinics, such as morphine and prednisolone. The anticholinergic drugs in node 2 were apparently different from those in nodes 3, 7 and 8, and their physicochemical properties may be different. It can be assumed that these drugs develop antimuscarinic effects through unknown antagonistic actions against the muscarinic receptor, or that they cause symptoms that are similar to anticholinergic effects but induced by a different pharmacological effect (i.e. not through the muscarinic receptor). However, further examination is needed to correctly evaluate this. The drugs in node 2 are nevertheless important to consider when assessing a patient’s anticholinergic burden, and they are defined as anticholinergics in anticholinergic rating scales. Further research is necessary in various areas, including basal pharmacological experiments concerning action at the muscarinic receptor.

These findings provide new information for the evaluation of anticholinergic effects independent of expert opinions or the experimental data included in anticholinergic rating scales. With the addition of this new information to current anticholinergic rating scales, the various problems indicated in a systematic review [3] may be resolved.

In this study, we constructed a discriminant model from a decision tree using a comparatively small dataset of descriptors produced by a single software package, for the easy interpretation of results. For methods based on quantitative structure-activity relationships, it is useful for the best model to be selected from several models constructed using various statistical methods, and to use integrated descriptors obtained from multiple software sources as input data [5]. If medical staff consider switching from one drug to another with the same effect but a lower anticholinergic burden, it is necessary for the strengths of the anticholinergic effect of each drug to be compared in a clinical setting. Therefore, an improved prediction model that incorporates anticholinergic effect strengths that vary among the anticholinergic rating scales is required, but this was not considered in this study. Taking the above problems into account, the current proposed method should be verified in clinical settings. If an improved prediction model of anticholinergic effects is constructed, the effect of drugs that do not appear in anticholinergic rating scales could be predicted, which might contribute to assessing a patient’s anticholinergic burden more precisely.

A prediction model has several limitations. First, the performance of the model depends on the data used in its construction; the model therefore has an application range that should not be ex-
ceeded. For example, we constructed our model using data from approved drugs, and these drugs are known to have common physicochemical properties, as implied by Lipinski’s Rule of 5. Consequently, our model is considered to be unsuitable for evaluating chemical compounds that cannot be used for medication. If a new drug that has a completely different structure from currently approved drugs is applied in clinical practice, predictions for this drug are difficult to make using our model because the structure of this drug was not included in the training dataset. Furthermore, prediction models potentially suffer from ‘overfitting’, meaning that they may have an extremely specific fit to the data used in their construction. Additionally, it is impossible to create predictions with 100% confidence for external data [5].

5. Conclusion

As long as it is used with these limitations in mind, our prediction model for the assessment of anticholinergic effects may be a useful reference tool for healthcare professionals considering a patient’s medications. We hope that with appropriate use of this model, patients’ anticholinergic burdens can be reduced, which should have a good effect on their quality of life and healthy life expectancy.

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Conflicts of Interest

All Authors declare that they have no conflict of interest associated with this manuscript.

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