

REVIEW

The Importance of Medicinal Chemistry Knowledge in the Clinical Pharmacist's Education

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Objective. To show why medicinal chemistry must be a key component of the education of pharmacy students, as well as in the pharmacist's practice.

Findings. Five case reports were selected by their clinically relevant elements of medicinal chemistry and were explained using structure-activity relationship data of the drugs involved in the case easily obtained from primary literature and in medicinal chemistry textbooks.

Summary. This paper demonstrates how critical clinical decisions can be addressed using medicinal chemistry knowledge. While such knowledge may not explain all clinical decisions, medicinal chemistry concepts are essential for the education of pharmacy students to explain drug action in general and clinical decisions.

Keywords: case studies, clinical chemistry, medicinal chemistry, pharmacy practice

INTRODUCTION

The International Union for Pure and Applied Chemistry (IUPAC) defines medicinal chemistry as a "chemistry-based discipline, also involving aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships."¹

In Brazil, medicinal chemistry is often called pharmaceutical chemistry. Pharmaceutical chemistry is a specific pharmacy area because its "emphasis is given on patient-focused pharmaceutical care and on the pharmacist as a therapeutic consultant, rather than a chemist."² Regardless of denomination, clinically relevant medicinal chemistry must be part of the formation of all pharmacy students, especially including those which are expected to work on clinical pharmacy.

Traditionally, pharmacy courses in Brazil present medicinal chemistry as a mandatory discipline, considered part of a pharmacist's formation together with other disciplines such as pharmacognosy, pharmaceuticals/pharmacotechnology, pharmacology and pharmaceutical care. Knowledge of medicinal chemistry is not only important

to a pharmacist's role as a member of the health care team, but also essential to the pharmacist's specific knowledge about medicines from other health care professionals.

The Brazilian National Curriculum Guidelines for the pharmacy courses define a pharmacist as one who must be capable to "act in all health care levels, based on scientific and intellectual rigor."³ These guidelines also state that pharmacy graduate courses must have key program contents such as "theoretical and practical knowledge related to research and development, production and quality assurance of pharmaceutical raw materials, ingredients and products," where medicinal chemistry is included. Moreover, among the 31 specific skills and competencies necessary to the formation of a pharmacist are the requirements that a pharmacist must be able, "to act in research, development, selection, manipulation, production, storage and quality control of ingredients, natural, synthetic and recombinant drugs, medicines, cosmetics, sanitizings and correlates" and "perform individual and collective pharmaceutical assistance." In relation to this, medicinal chemistry contributes to a pharmacist's drug design and development skills, and knowledge of structure-activity relationships (SAR), thereby enabling a pharmacist to perform in adverse reactions management and pharmaceutical care.

In 2013, the Brazilian Federal Council of Pharmacy (FCP) published resolution #586.⁴ The FCP regulates independent pharmacists' prescribing authority in Brazil, and assigns new responsibilities to pharmacists. Independent pharmacists' drug prescribing authority can be

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defined as the exercise of drug prescribing by a pharmacist autonomously within his/her clinical competence. This practice is implemented in several countries worldwide, such as Canada, UK, South Africa and Australia.⁵⁻⁸

Medicinal chemistry discipline in pharmacy curriculum plays an important role in the construction of a specific knowledge of a pharmacist from other prescribers regarding pharmacotherapy. Pharmacy students must use medicinal chemistry concepts as one of the determinants of pharmacotherapy decisions, especially the SAR background of the involved drugs, to achieve a high-level practice on clinical pharmacy. Several papers published in this *Journal* reported on this topic. Khan and colleagues,⁹ Alsharif and colleagues,¹⁰ and Beleh and colleagues,¹¹ emphasized the importance of medicinal chemistry knowledge for pharmacy students. Moreover, this can be noted by the shift in classical textbooks of medicinal chemistry such as those by Lemke and colleagues,² and Currie and colleagues¹² that emphasize the clinical relevance of the discipline and which have been adopted by many medicinal chemistry courses around the world.

Thus, the aim of this paper is to show examples of how medicinal chemistry can be helpful in pharmacotherapy decisions through a review of case reports in the literature and application of medicinal chemistry concepts to elaborate and explain the clinical decision made in each case.

METHODS

The author searched the PubMed database for case reports using the keywords: propranolol and psychosis, timolol and bronchoconstriction, tetracaine and allergy, atorvastatin and rhabdomyolysis, diphenhydramine and extrapyramidal. These keywords were suggested by an experienced medicinal chemist who was familiar with the topic.

The case reports were adapted to focus on the main aspects of the study, but their overall meaning was retained. Some specific information was maintained to keep the cases Relevant to the practice of pharmacy. Trade names, personal data and other irrelevant information were excluded.

The clinical case reports were evaluated using the SAR data from didactical books used in medicinal chemistry courses.^{2,12,13} The case studies must state the importance of medicinal chemistry concepts in line with other relevant clinical aspects of a pharmacist's knowledge in the prevention or management of such cases.

RESULTS AND DISCUSSION

Case report 1: Propranolol-induced psychosis (adapted from Cunnane and Blackwood¹⁴)

"A 21-year old man with a history of migraine was treated with oral propranolol for 9 months. This gave

inadequate prophylaxis and the dose was therefore increased. No further attacks occurred. After several weeks at the higher dose he began to experience visual hallucinations involving spiders, auditory hallucinations in which a voice whispered his name, vivid, recurrent nightmares, depressed mood with suicidal impulses, and personality change with odd behavior and violent outbursts. He had no previous psychiatric history and an even-tempered, outgoing premorbid personality.

On admission to the hospital, propranolol was discontinued and his symptoms improved markedly. Physical examination was normal, and no other medication was given. Electroencephalogram and skull radiograph were normal, as well as hematological and biochemical investigations. He remained improved for 5 more days before discharge."

Propranolol (Figure 1) is a well-known drug that acts as antagonist of adrenergic β -receptors ($A\beta R$).^{2,13} The drug produces reduction of blood pressure by the antagonism of β_1 receptors located in renal and cardiac tissues, leading to decreased rennin secretion and negative chronotropic and inotropic effects, respectively. This characteristic allows its use in the treatment of several cardiovascular diseases, such as hypertension and angina pectoris. However, propranolol is a non-selective $A\beta R$ antagonist, as well as timolol. The β_2 receptors blocked by these drugs can cause bronchial effects due to bronchoconstriction. Patients previously diagnosed with asthma, chronic obstructive pulmonary disease (COPD) and other bronchoreactivity-related conditions should not use these drugs.¹³ In counterpart, the β_2 receptors blockade may be useful in treating migraine,¹⁵ since the β_2 receptors located in brain vessels are involved in vasodilation. The $A\beta R$ are also found in the central nervous system (CNS), where they are involved in mood regulation.¹³ Several reports determine the relationship between propranolol use and CNS effects,¹⁶ with the case report above as an example.

Analyzing the physicochemical properties of propranolol, timolol, metoprolol and betaxolol (Figure 1), it is possible to verify that these molecules are highly lipophilic.¹⁷ This lipophilicity can be verified by the carbon atom count to heteroatom count (mainly those with hydrogen attached, such as NHs and OHs) ratio. Empirical prediction of lipophilicity is explained in primary medical chemistry literature.² Polar groups, especially NHs and OHs, increase the hydrophilicity. The more carbons present in the compound, the more lipophilic the molecule. Thus, all the presented molecules in Figure 1 can be considered lipophilic. The relationship between lipophilicity and crossing blood-brain barrier (BBB) capacity has been reported,¹⁸ showing high positive

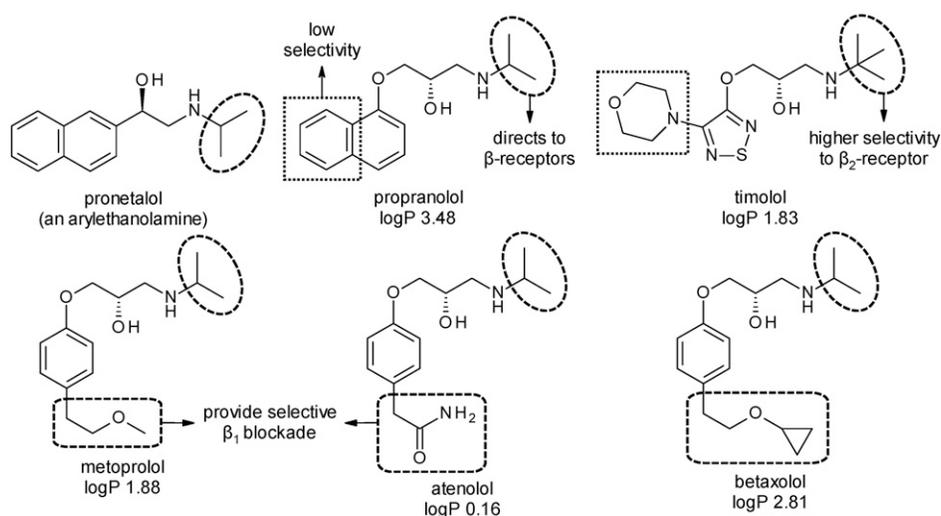


Figure 1. Beta-blockers Widely Used in Therapeutics. SAR data are summarized by the ellipses (β -directing group), dotted squares (reduces β -receptor selectivity) and dashed rectangles (β_1 -directing group).

correlation between logP values and BBB penetration, i.e., the more lipophilic the molecule, the higher the BBB penetration. Thus, propranolol can easily cross the BBB and block the $A\beta R$ in CNS, leading to behavioral effects such as depression and psychosis.¹⁶

The use of more hydrophilic drugs could prevent these effects. Atenolol (Figure 1) is an $A\beta R$ antagonist less lipophilic (or more hydrophilic) than propranolol, due to the presence of a polar amide group and absence of one benzene ring.¹⁷ This manner, atenolol could be an option to avoid the CNS effects, since it poorly penetrates BBB, as can be seen in the study from Westerlund.¹⁹ This case illustrates the physicochemical properties of drugs with an important effect that could be handled by a pharmacist trained in medicinal chemistry. Moreover, this shows the importance of knowing drug adverse effects in developing new $A\beta R$ antagonists more hydrophilic, and also as a guide to rational selection of $A\beta R$ antagonists in cases where CNS effects should be avoided.

Case report 2: Respiratory arrest by ophthalmic timolol (adapted from Prince and Carliner²⁰)

“A 67-year old man had been receiving treatment for chronic obstructive pulmonary disease, noncritical calcific aortic stenosis, essential hypertension, and glaucoma, which included hydrochlorothiazide, theophylline and metaproterenol sulfate (an inhaler) as pharmacotherapy. Pulmonary function tests performed seven months prior to admission demonstrated moderate obstructive disease with air trapping. The forced vital capacity was 3.2 L, and the forced expiratory volume in one second was 1.76 L (55 %). There was no significant change in flow rate following the administration of bronchodilator drugs. He

had been clinically stable, except for worsening glaucoma despite pilocarpine therapy.

On the day of admission, he had been seen in the ophthalmology clinic, and because of progression of glaucoma, timolol ophthalmic solution was prescribed. That evening, within approximately five minutes of his first dose of one drop in each eye, he noted the acute onset of shortness of breath. His symptoms were not relieved by three of four puffs from metaproterenol. In minutes, his dyspnea progressed rapidly, and he was getting cyanotic. When paramedics arrived, the patient was unresponsive and apneic. Assisted ventilation and oxygen were begun during his transference to the hospital.

When he arrived in the emergency room, there was no effective spontaneous respiration, and intubation was performed. Forty minutes after intubation and treatment, he was adequately responsive and extubated 15 hours later.”

$A\beta R$ antagonists, such as timolol, are widely used in glaucoma therapy due to their capacity to reduce the intraocular pressure. This effect results from the blockade of adrenergic β_1 receptor in the eye, which leads to lowered aqueous humor production.²¹ Other $A\beta R$ antagonists used in glaucoma therapy are levobunolol, metipranolol, betaxolol and carteolol. $A\beta R$ antagonists induce bronchoconstriction due to adrenergic β_2 receptor blockade in lungs, since adrenergic β_2 receptors that are expressed in the bronchial tissues cause bronchodilation. In the presented case, the blockade of these receptors was responsible for the bronchoconstriction in the patient, otherwise this effect should be solved using an adrenergic β_2 receptor antagonist (metaproterenol). To avoid this issue, β_1 -selective antagonists are necessary.¹³

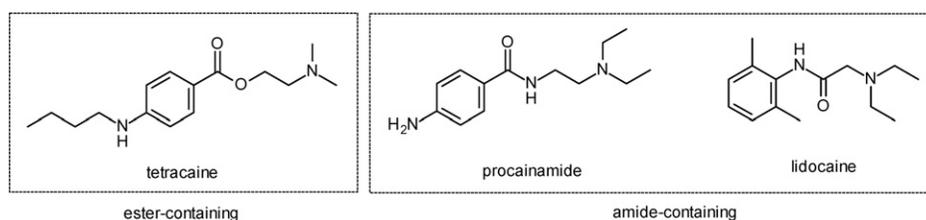


Figure 2. Examples of Local Anesthetics. Tetracaine is a quickly hydrolysed ester-containing anesthetic (left rectangle), while the amide-containing (right rectangle) such as Procainamide and Lidocaine are metabolically more stable.

A β R antagonists are aryloxypropanolamine or aryloethanolamine substituted compounds. Although all aryloethanolamines antagonists (such as pronetolol, Figure 1) are non-selective β -blockers, the aryloxypropanolamines can be made selective by adding a 4-substituent on the aromatic ring. SAR data for A β R antagonists presenting aryloxypropanolamine structure² defines that non-selective A β R antagonists clinically available are generally substituted in the 2 and/or 3-position of the phenoxy group. This substitution pattern in propranolol and timolol does not lead to any selectivity to adrenergic β_1 receptor located in the eye. Moreover, the *tert*-butyl group in timolol increases the activity in β_2 receptor. β_1 -Selective molecules present a substituent in the 4 position of the aromatic ring, which improves the β_1 -selectivity through steric hindrance to β_2 receptor binding.² Polarity in this substituent changes the lipophilicity and therefore the pharmacokinetic profile, and small 2-substituents usually do not affect the β_1 -selectivity. Atenolol, metoprolol and betaxolol are examples of adrenergic β_1 -receptor selective blockers. But how could eyedrops lead to this respiratory arrest?

To achieve the therapeutic effect in glaucoma, the administered drug must penetrate the ocular barrier, and consequently must be considerably lipophilic.²¹ However, lipophilic molecules can be absorbed significantly by the organism even in topical administration, reaching the systemic circulation in considerable concentration.²² The administration of a classical β_1 -selective antagonist such as atenolol would not solve the problem due to its more hydrophilic characteristic (Figure 1), which impairs its penetration through the eye. In this case, a lipophilic β_1 -selective antagonist (such as betaxolol) would avoid the respiratory impairment and achieve adequate concentrations inside the eye to treat glaucoma.¹³ Betaxolol will remain in the lipophilic layer of the membrane due to its lipophilicity, avoiding the systemic distribution and thus potential side effects. Moreover, betaxolol also possess the β_1 directing group that avoids the effect on bronchial β_2 -receptor. A simple analysis of the structures of atenolol and betaxolol by a clinical pharmacist using its

medicinal chemistry knowledge would lead to this conclusion.

Case report 3: Allergic contact dermatitis caused by tetracaine (adapted from García-Gavin and colleagues²³)

“An 89-year-old non-atopic woman was referred with a 15-day history of pruritic lesions affecting her ears and periauricular areas that began after she had started to use optic drops containing tetracaine, which had been prescribed to treat cold-related otalgia. Allergy test was conducted; this resulted in a strong response to the product and to local anesthetic blend present in a commercial allergy test. This mixture contains benzocaine, tetracaine hydrochloride, and dibucaine hydrochloride. The medicine contained tetracaine hydrochloride, phenol, menthol, benzalkonium chloride, and clove oil. Patch test results showed only a strong response to tetracaine hydrochloride. When the patient stopped using the product, her dermatitis healed after a 1-week treatment with topical steroids.”

Local anesthetics are frequently related to allergic reactions. Although there are several complains from allergic reactions after anesthesia, there are evidence that allergy to local anesthetics are quite low.²⁴ However, this reaction is more frequently associated to the administration of ester-containing local anesthetics²⁵ such as tetracaine, benzocaine and procaine.

4-Aminobenzoic acid (also known as PABA) and other benzoic acid derivatives are considered strong sensitizers of the skin.²⁶ PABA is commonly used as photoprotection agent in sunscreens, being widely known for causing allergy.²⁷ Moreover, people who are allergic to PABA are frequently allergic to other benzoic acid derivatives such as aspirin, parabens and other drugs.²⁸

Local anesthetics such as tetracaine are drugs widely used in surgical and other pain control such as otalgia. Chemically, they possess three distinct moieties in their molecules: an aromatic ring and a hydrophilic group (generally a tertiary amine) connected through a carbonyl group. Since the connecting group can be an ester or an amide, local anesthetics are classically grouped in ester-containing and amide-containing molecules (Figure 2).^{2,29}

These groups play the role in the metabolic stability of the drugs, where the ester-containing molecules generally possess shorter half-life than the amide-containing due to higher hydrolysis rate by unspecific esterases or cholinesterases.³⁰

Tetracaine is an ester-containing local anesthetic which presents a 4-(butylamino)phenyl ring in its aromatic moiety. This group ensures the high potency attributed to tetracaine, since 4-butylamino group is electron-donating, increasing the electronic density in the ester carbonyl, which is an important pharmacophore to sodium channel interaction.² After biotransformation, tetracaine is hydrolyzed to 4-aminobenzoic acid (PABA), which is devoid of anesthetic activity (Figure 3).

The allergy was most likely caused by PABA and not by the drug itself and a simple analysis of the structure of tetracaine and other local anesthetics (such as benzocaine) can explain the possibility of PABA production after drug hydrolysis *in vivo*. This kind of allergy was already reported in a systematic review.²⁵ Knowledge of clinically relevant medicinal chemistry is necessary to achieve such conclusion.

Case report 4: Atorvastatin-related rhabdomyolysis (adapted from Holbrook and colleagues³¹)

“A 58-year-old white man presented to a community hospital emergency with a sudden-onset retrosternal chest discomfort associated with presyncope and diaphoresis. Past medical history included hypertension and dyslipidemia but no medications. He was an occasional smoker and consumed 12-14 drinks of beer weekly. Based on his electrocardiogram results and troponin level, he was diagnosed as having an inferior ST-elevation myocardial

infarction. He underwent reperfusion with tenecteplase, and started on aspirin, atorvastatin and ramipril daily and referred to cardiology center for an urgent cardiac catheterization. Creatine kinase (CK) peak level at the time of ST-elevation myocardial infarction was 442 U/L.

Some weeks later, the patient was referred to the doctor with the complaint of 2 weeks of worsening generalized myalgias, nausea and vomiting, and fatigue and malaise to the point that he could not walk adequately. He used to exercise regularly and had completed a marathon several years earlier without such muscle symptoms. He also reported brown urine, although no recent history of trauma or extreme physical exertion was reported. Physical examination was unremarkable other than a well-healed sternal scar and reduced power in both upper and lower extremities. Initial laboratory results revealed urea of 31.9 mM, serum creatinine of 316 μ M, aspartate aminotransferase (AST) of 3689 U/L, alanine aminotransferase (ALT) of 1962 U/L, CK of 141,940 U/L, international normalized ratio of 5.1. Urine sample was positive for myoglobin.

Atorvastatin was discontinued and intravenous fluids and mannitol were initiated, as well as hemodialysis. Serum creatinine and CK levels peaked 3 days after admission, reaching 489 μ mol/L and 166,122 U/L, respectively, and then declined over the following 2 weeks, at which time dialysis was discontinued. The patient was discharged with a serum creatinine of 241 μ mol/L and CK of 195 U/L. The patient’s AST and ALT levels had also declined to 205 and 55 U/L, respectively.”

Cholesterol is the most important steroid found in animal cells, including humans. This sterol is an essential structural component of cell membrane, required to maintain its integrity and adequate fluidity.³² Moreover,

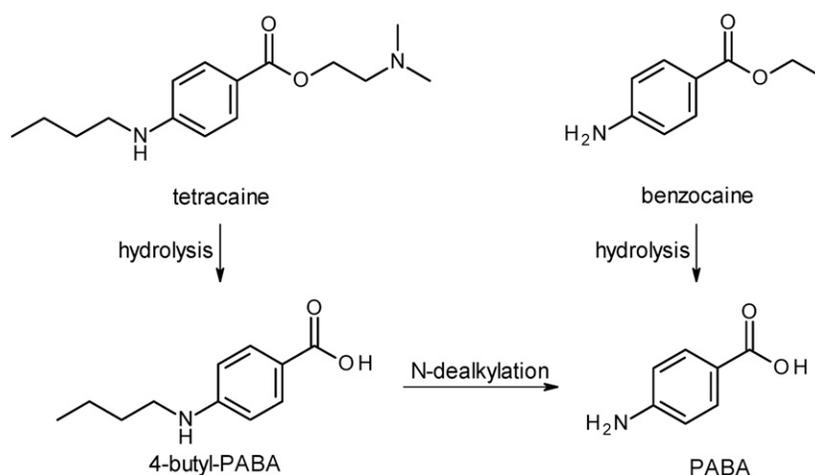


Figure 3. Biotransformation of Tetracaine and Benzocaine to PABA. The hydrolysis of both ester anesthetics (and further dealkylation, in case of Tetracaine) leads to PABA, the allergenic compound.

cholesterol is the starting material to the steroid hormones and bile acids.³³ However, hypercholesterolemia is strongly associated with cardiovascular disease, since it increases the development of atherosclerosis.³⁴ As 3-hydroxy-3-methylglutaryl-coenzyme-A (HMGCoA) conversion to mevalonate by the enzyme HMGCoA reductase is the main step in the human cholesterol biosynthesis, inhibitors of this key enzyme (eg, statins) are among the most important drugs in the treatment of cardiovascular disease. Consequently, statins are always present among the top selling drugs in the world, being atorvastatin the best example of blockbuster statin.³⁵

To reduce cholesterol levels, statins must interfere mainly with hepatic cholesterol production rather than other tissues (especially the muscles). Albeit cholesterol can be synthesized virtually by any other tissue, liver is the main producer of cholesterol. The most important statin-related adverse effects are myopathies, comprising myalgia and rarely (but dangerous) rhabdomyolysis. Myopathy-related effects can be assessed by CK serum levels,³¹ as what happened to the patient in this case, which presented CK serum level of 166,122 U/L. The higher the CK serum level, the more likely the myopathies will occur. Patient's urine was brown due to the presence of myoglobin originated muscle breakdown (rhabdomyolysis). This

effect is closely related to inhibition of ubiquinone (coenzyme Q10) biosynthesis, which also depends on HMGCoA reductase activity, and to the hyperexcitability of skeletal muscle caused by lowered cholesterol levels in muscle cells.³¹ Thus, liver-directed statins are less prone to cause myopathies, and this must be considered when designing safer statins.³⁶

To achieve liver-directed effect, the statin molecule should be more hydrophilic. White showed the correlation between $\log D_{7.4}$ (the distribution coefficient *n*-octanol/water in pH 7.4) and the potential to cause myopathies.³⁷ More hydrophilic statins (such as rosuvastatin and pravastatin) are more likely taken up by the liver organic anion transport polypeptide (OATP) and are less distributed to the extra-hepatic tissues, while the more lipophilic statins (as atorvastatin, simvastatin and cerivastatin) are frequently linked to myopathies cases due to its higher extra-hepatic concentrations (Figure 4).³⁷ In fact, cerivastatin was withdrawn from the market because it caused serious adverse effects, especially those related to myopathies.

The lipophilicity of these molecules can also be assessed using the empirical carbon/heteroatom ratio approach discussed previously. The non-lactonized carboxylic acid, in addition to the sulfonamide group present in

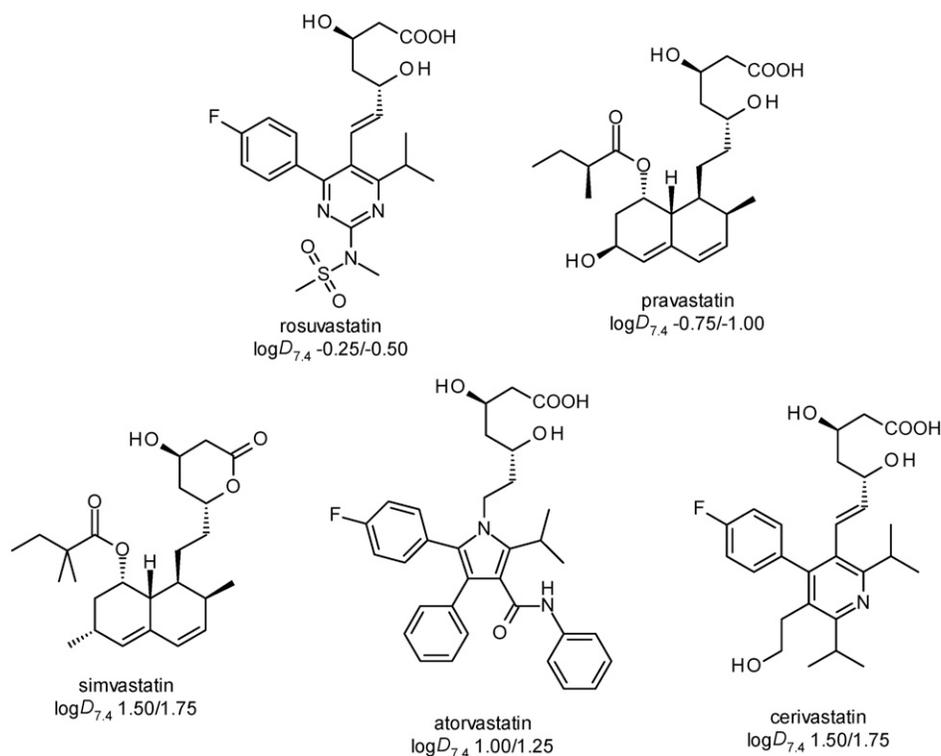


Figure 4. Statins and their $\text{Log}D_{7.4}$ Values. The $\text{Log}D_{7.4}$ values indicate the apparent lipophilicity in the physiological pH. Negative $\text{Log}D_{7.4}$ values represent hydrophilic molecules (Rosuvastatin and Pravastatin), while positive values suggest high lipophilicity (Simvastatin, Atorvastatin and Cerivastatin).

rosuvastatin and the hydroxyl present in pravastatin, helps to decrease the lipophilicity of these two molecules and to avoid the extra-hepatic effects. In contrast, the more lipophilic statins (such as simvastatin, atorvastatin and cerivastatin) lack these additional polar groups. In summary, the administration of a more hydrophilic statin instead of atorvastatin would avoid the occurrence of rhabdomyolysis. However, only the molecular-directed therapeutic choice using concepts of lipophilicity (provided by medicinal chemistry), as discussed in the first case study, can evaluate these potentials.

Case 5: Diphenhydramine-induced excitation (adapted from Cheng and colleagues³⁸)

“A 46-year-old woman diagnosed with recurrent left breast cancer with pulmonary metastasis was treated in an outpatient setting for her first cycle of paclitaxel. Before starting chemotherapy, she received premedication in the following sequence: ranitidine, diphenhydramine, dexamethasone and ondansetron, all intravenously administered. Within 5-10 minutes after receiving diphenhydramine, the nurses noted the patient was becoming very agitated, but with no tremor or confusion. Although the woman was agitated, this did not interrupt the administration of the rest of the premedications and chemotherapy. Vital signs were normal.

The patient reported she was well before receiving the intravenous premedications, but after she received diphenhydramine, she felt that she could not sit down, and felt better when she stood and walked around. She walked around the room and in the hallway for the 3-hour of chemotherapy infusion. The patient denied tremors or hallucinations, and said that the agitation resolved toward the end of the chemotherapy session. Once she returned

home, she fell asleep and awoke with no residual feelings of agitation.

For the second cycle of paclitaxel the next month, diphenhydramine was substituted by hydroxyzine, but otherwise the same premedication regimen was administered. This time no agitation was observed in the patient. Follow-up was discontinued after the second cycle due to the patient’s poor response to paclitaxel.”

Akathisia (eg, agitation, excitation) is characterized by physical restlessness and a subjective urge to move.³⁹ It is also a neurological side effect mainly of antipsychotic medications, although it can occur following administration of other psychotropic drugs, such as antidepressants and antiemetics, and after withdrawal of certain drugs, as opioid, barbiturates and cocaine. It is proposed that akathisia mainly involves the blockade of dopaminergic transmission in the CNS. This is corroborated by its association with Parkinson’s disease.⁴⁰ Moreover, increased level of norepinephrine (which is associated with mechanisms that regulate aggressiveness, alertness, and arousal) is observed in people who experience akathisia.⁴¹ Further evidence also suggest participation of the cholinergic system in akathisia, since some anticholinergic drugs can induce this effect, and the administration of physostigmine (an anticholinesterase agent) is useful to reverse these cases.⁴² Although the patient was taking several medications, in this case the excitatory effect was attributed to diphenhydramine because after changing this drug to hydroxyzine (another antihistamine), and maintaining all the other medications, the excitatory effect was gone.

Diphenhydramine is a classical antagonist of H₁ receptor (antihistamine), which is widely used (as other antihistamines) to avoid histaminergic effects, especially those related to allergic reactions (Figure 5).

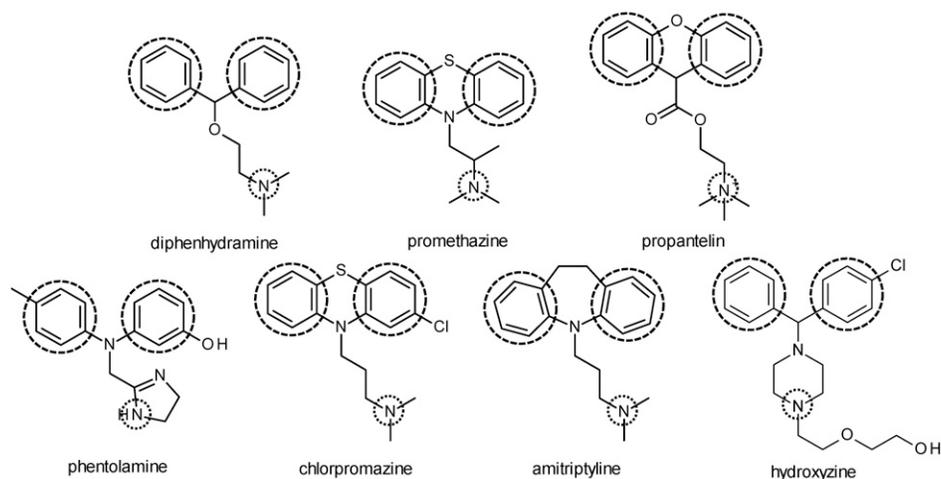


Figure 5. Similarities Among Antihistamines and Other Drugs. Note that all the molecules present two aromatic rings (dashed circles) and a basic nitrogen (dotted circle) in similar positions in the space.

Antihistamines are traditionally classified in two “generations.” The first generation is composed by drugs which cause intense sedative effects attributed to H₁ receptor blockade in the CNS, while the second generation comprises molecules that are by purpose less lipophilic to avoid the penetration through BBB.²

Antihistamines are frequently related to several side effects such as dry mouth, urinary retention, sedation, drowsiness and decreased cognitive ability.¹³ As classical antihistamines are lipophilic molecules (including diphenhydramine), they can easily cross the BBB and cause CNS effects. But considering that antihistamines cause sedative effects, how can diphenhydramine cause excitation?

Antihistamines are highly promiscuous drugs (ie, capable to bind to several receptors), which can interact to cholinergic muscarinic, α -adrenergic, dopaminergic and serotonergic receptors, besides histaminergic receptors.¹³ This promiscuity is easily observed in the structural characteristics of antihistamines by an experienced medicinal chemist. Diphenhydramine and promethazine (another example of highly promiscuous antihistamine) are chemically close to propanthelin (antimuscarinic), phentolamine (α -adrenergic blocker), chlorpromazine (dopaminergic blocker) and amitriptyline (antidepressant). These molecules present two aromatic rings linked to a spacer group which presents a nitrogen atom (basic or positively charged as ammonium, Figure 5). Thus, diphenhydramine shares several pharmacological effects to these drugs.^{2,13} Drug-induced akathisia is frequently related to antipsychotic and antidepressant drugs such as chlorpromazine and amitriptyline. Considering the similarity of diphenhydramine and these molecules, the potential to cause akathisia is evident. However, agitation is also common after the administration of certain anticholinergic drugs.⁴² Regarding the antimuscarinic activity, diphenhydramine and other ethanalamine antihistamines are highly similar to anticholinergic drugs because they possess the oxygen atom that allows the same interactions that acetylcholine does. It is expected that diphenhydramine administration leads to anticholinergic side effects. The administration of hydroxyzine did not lead to the agitation effect, possibly because hydroxyzine lacks important affinity for the muscarinic receptor,⁴³ due to the absence of the oxygen atom (which reduces the similarity to acetylcholine), the presence of chlorine atom (to improve selectivity to H₁ receptor) and also the hydroxyl group (increasing the hydrophilicity and therefore lowering the BBB penetration).² In the original case report, the authors discuss if this condition was caused by the antidopaminergic or the anticholinergic effects of diphenhydramine, but independent of which mechanism is

involved, both are plausible and hence this situation is considered quite predictable to a pharmacist experienced in medicinal chemistry.

CONCLUSION

The five case studies presented in this paper showed the importance of clinically relevant medicinal chemistry knowledge in the training of all pharmacists (but especially those who work in clinical pharmacy) and how the clinical outcomes of each case can be thoroughly explained by drug structure. Considering the importance of medicinal chemistry as a mandatory discipline to the pharmacist's graduation and successful practice should provide specific knowledge beyond drug design and discovery skills and should be linked to clinical content that will distinguish the pharmacist from other health care professionals.

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