Update review

Classification of antiarrhythmic agents and the two laws of pharmacology

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1. Introduction

In a standard textbook of pharmacology [1] there are 50 (three-column, 69-line) pages in the index (50×3×69 = 10 350). In order to render this vast information somewhat manageable the chemicals are grouped in about 50 chapters, one of which is “Agents used in cardiac arrhythmias” [2]. Antiarrhythmic agents are in turn subdivided in four classes plus a group of miscellaneous agents (containing those that do not fit in any of the four standard classes). At times it is desirable to subdivide these classes into subclasses (main topic of this paper).

Although such classification renders the pharmacological information more manageable, it is frequently difficult or impossible to fit a chemical in a class. For example, while beta blockers certainly belong as a chapter in the section on autonomic drugs, they also form an important class in the antiarrhythmic agents (see below). In addition, they also need to be described in the sections on angina, congestive heart failure and hypertension (among others). This problem follows directly from the first law of pharmacology: no drug has a single effect.

A group of investigators has tried to remedy this problem for classification of antiarrhythmic agents by proposing an alternative: the Sicilian gambit [3]. Basically, they list all the chemicals with antiarrhythmic properties as rows in a table, while describing all possible actions in columns. The advantage of this system is that it can be very accurate and complete: as new chemicals emerge new rows are added, while new mechanisms are added as new columns. Unfortunately, as progress is made the complexity of the table grows nearly quadratically and soon the entries exceed the retention capacity of ordinary souls . . .

2. Class I

These are agents that block sodium channels as their primary mechanism of action. As a result, they depress the maximum rate of rise (\( v_{\text{max}} \)) of the cardiac action potential (AP) and slow conduction through the His–Purkinje system as well as the atrial and ventricular myocardium. However, the depressant actions of these agents vary quite widely, so that Hoffman and Bigger [5] divided them into two subclasses: (A) depresses conduction and lengthens the AP duration (APD), while (B) has little effect or actually increases conduction and shortens the APD. In the eighties some new sodium channel blockers were introduced that were much more potent in depressing conduction, but they did very little to APD. So, it was deemed necessary to introduce a new subclass: class IC [6].

Campbell [7] noted that the class IC agents differed from the other class I drugs:

\[
\text{they demonstrated progressive enhancement of their depressive effects (on } v_{\text{max}} \text{) with increasing frequency of stimulation (rate-dependent block) but the rate at which } v_{\text{max}} \text{ declined to its new level following a sudden increase in frequency was found to be much slower than reported for other class I drugs in clinical use}
\]

(see Fig. 1).

In concentrations that similarly reduced \( v_{\text{max}} \), Campbell published in this Journal that the three subclasses of sodium channel blockers had markedly differing electro-
Subclassification of Class I antiarrhythmic drugs

Subclassi®cation of Class I antiarrhythmic drugs can more effectively increase the effective refractory period (ERP)/APD.

3. Class II

These are agents that act by blocking β-receptors. This mechanism is the only antiarrhythmic action that has been documented to be effective in prolonging life [9] and thereby is the only class that has satisfied the second law of pharmacology: primum non nocere. Indeed, class I (CAST [10]) and class III (SWORD [11]) agents have been shown to cause excess mortality in patients where a benefit was expected. While for class IV agents the large trials are still in progress, there certainly exist warning flags against their general wide spread use [12].

As for the other classes, it has been shown that β-Blockers can also be subdivided into two classes: β1-blockers, which selectively block the β-receptors in the heart; and β2-blockers, that do not exhibit any cardiac selectivity.

4. Class III

These are agents that act by lengthening the APD and thereby the effective refractory (e.g., sotalol).

4.1. Class III

While these agents usually lengthen the APD at normal and slow heart rates, the prolongation frequently declines as the cycle length is reduced. As a result, the prolongation of APD is marked when it is not needed, but vanishes during tachycardia: reverse use-dependence (Fig. 2). Following long cycle lengths the prolongation of the APD can be so excessive that repolarization disturbances occur: hesitation of repolarization, EADs, torsades de pointes and fibrillation. In addition, reverse use-dependence induces instability of APD: following an ectopic, the next diastolic interval is shorter or longer (compensatory pause). Reverse use-dependence shortens the APD following a short diastolic interval. But, at a given cycle length, a shorter APD

physiological properties (Table 1 summarizes the Campbell results).

In 1977, Hondeghem and Katzung [8] described the molecular mechanisms of how sodium channel blocking antiarrhythmic agents interact with their receptor (modulated receptor theory). Briefly, during each upstroke and/or plateau block develops, while during diastole unblocking proceeds. Hence, if recovery from block is slow, then during a normal diastolic interval there can be only little recovery. For this reason there can be only little block during the AP, otherwise accumulation of block would lead to toxicity. However, if recovery from block is fast, then there can be much more unblocking during diastole . . . and much more block during the AP is also permissible. By these mechanisms Campbell reasoned that fast recovering agents can more effectively increase the effective refractory period (ERP)/APD.

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Table 1
Summary of Campbell results (Ref. [7])

<table>
<thead>
<tr>
<th>Class</th>
<th>Iα</th>
<th>Iβ</th>
<th>Iγ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of depression of ( \dot{\nu}_{max} ) (per action potential)</td>
<td>Intermediate</td>
<td>Fast</td>
<td>Slow</td>
</tr>
<tr>
<td>APD</td>
<td>0.05 &lt; AP &lt; 0.2</td>
<td>AP &gt; 0.2</td>
<td>AP &gt; 0.05</td>
</tr>
<tr>
<td>ERP</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Increase ERP/APD</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Recovery from block</td>
<td>2–12 s</td>
<td>200–500 ms</td>
<td>&gt; 12 s</td>
</tr>
<tr>
<td>Examples</td>
<td>Disopyramide</td>
<td>Lidocaine</td>
<td>Encaïnide</td>
</tr>
<tr>
<td></td>
<td>Procaïnamide</td>
<td>Mexillette</td>
<td>Flecaïnide</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>Toçainide</td>
<td>Lorcaïnide</td>
</tr>
</tbody>
</table>
leads to a longer diastolic interval, which in turn provides for a longer APD followed by a shorter diastole, etc., etc., ... in this way reverse use-dependence leads to APD alternans and chaos. As a result these agents have been predicted and observed [11,13] to have a low efficacy and to be proarrhythmic. I have proposed that the class III agents which act primarily during bradycardia be grouped as class III_b [15].

4.2. Class III_a

It follows that ideally a class III agent should upon tachycardia use-dependently lengthen the APD until the effective refractory period exceeds the cycle length of the tachycardia, i.e., rendering continuation of the tachycardia impossible. I have suggested that agents which act primarily upon acceleration of the heart would be classified as class III_a. Class III_a agents would act like a chemical defibrillator [16]: have little effect during normal sinus rhythm, but vigorously interfere with a tachycardia. Unfortunately, there are no such agents available yet for clinical use.

4.3. Class III_ab

Of all the class III antiarrhythmic agents, amiodarone appears to have the greatest efficacy and appears to trigger the least torsades de pointes. It is also the agent that lengthens the APD about equally well at short as at long cycle lengths, hence class III_ab. Maintenance of the prolongation during tachycardia renders the agent more effective, while not excessively prolonging the APD following long cycle lengths reduces the likelihood of proarrhythmia.

As noted above, no drug has a single effect, this is especially true for amiodarone that belongs to all four classes of antiarrhythmic action: not only does it lengthen APD (class III), it also blocks sodium channels (class I), has antiadrenergic actions (class II) and blocks calcium channels (class IV). The sodium and calcium channel block may help prevent repolarization disturbances (during crossing of the calcium and sodium window currents), while the antiadrenergic effect may contribute to its general beneficial effect.

5. Class IV

These are agents that act by blocking calcium channels. Similar to sodium channel blockers, these agents bind preferentially during the upstroke and/or the plateau of the cardiac AP while they unblock primarily during diastole [16]. Similar to the proposal by Campbell [7] for sodium channels, one could also subdivide the calcium channel blockers into relatively slow recovering agents (class IV_a) and fast recovering blockers (class IV_b).

Calcium channel blocking agents that exhibit slow recovery from block (class IV_a, e.g., verapamil and diltiazem) accumulate proportionally to heart rate. By this mechanism they can interfere with tachycardias that involve reentry conduction in nodal tissues. Class IV_b (e.g., dihydropyridine calcium channel blocking agents) have little antiarrhythmic activity, because their dissociation rate constant from cardiac calcium channels is so short that little drug remains on the receptors by the end of diastole.

6. Conclusion

Kinetic aspects of interactions of antiarrhythmic agents with their ion channels, as pointed out by Campbell [7], are clearly important in the classification, understanding
and effective use of antiarrhythmic agents. Grouping of
drugs into classes inherently simplifies by making the
agents look more similar than they really are. It is therefore
important that all the differences also be tabulated in an
encyclopedic fashion [3], so that we are reminded of the
first law of pharmacology. Most importantly, classification
of a drug based upon a primary effect (which inherently
proves its efficacy), does not render it safe: large scale use
should not start following classification, but should await
satisfaction of the second law of pharmacology.

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