Sotalol: a fool’s deal?

See page 1504 for the article to which this Editorial refers

Curiously, dl-sotalol is largely used in the maintenance of sinus rhythm after conversion of atrial fibrillation, although its greater efficacy compared to pure beta-blockers has never been established. The article by Plewan et al. in this issue is a good opportunity to formulate some reflections about its efficacy compared to beta-blockers, and to make some remarks about the ways we prescribe antiarrhythmic agents and evaluate their effects.

Many studies have been published about the antiarrhythmic efficacy of sotalol. Most often, however, sotalol was compared to placebo, and the better efficacy of the active drug was attributed to its type III effect rather than to its ability to block beta-adrenergic receptors. Until recently, no comparison was attempted with the reference type III drug that should be amiodarone. When such a comparison was done in permanent atrial fibrillation the evident superiority of the reference drug was verified. This information was no big surprise for experienced clinicians.

References


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Another potential mechanism of action of dl-sotalol is its beta-blocking effect, and here too there are few comparisons in the literature between sotalol and any beta-blocker at the atrial level. This means that while sotalol is credited with the added value of its type III action there is no definite evidence that such a belief is justified. It should be recalled that when Vaughan-Williams proposed his still current classification, sotalol was not available and amiodarone was alone in its class. Vaughan-Williams nevertheless took the trouble to specify that, in his opinion any beta-blocker (type II effect) by definition also had a type III effect of prolonging the plateau of the cellular action potential. The generally admitted opinion about the antiarrhythmic action of beta-blockers in atrial fibrillation is that there is no clear evidence that they are useful, with the exception of the postoperative period.

Several questions are raised by the study of Plewan et al. Why does the present experience provide evidence that beta-blockers are effective in the prevention of the recurrence of atrial fibrillation, and why did it take so long? Why is there no evidence that sotalol does not do better than a beta-blocker? Are there different and specific indications for type II and type III effects in the treatment of atrial fibrillation? How can we be precise about these and how can we differentiate the beta-blocking effect from the type III action in the evaluation of the pharmacological effect?

Atrial fibrillation is a well defined arrhythmia but by no means a homogeneous entity. For more than a decade particular attention has been paid, not only to its potentially severe thrombo-embolic complications and contribution to heart failure, but also to its various mechanisms. Atrial fibrillation can be a primary arrhythmia but more often it results from the deterioration of electrophysiological conditions provoked by atrial arrhythmias, such as flutter or automatic foci preferentially located in the pulmonary veins, or even junctional reciprocating tachycardias, not to mention ventricular tachycardias that may occasionally trigger atrial fibrillation. The fibrillatory process can occur in an atrial tissue altered by valvular disease or cardiomyopathy which then appears as the aetiology. It may also occur in a heart disease which may not necessarily be the direct cause of the arrhythmia. In coronary artery disease or hypertension, the cause-to-effect relationship with atrial fibrillation is not necessarily established, but the context of heart disease is important for the choice of drugs. Finally, the absence of any structural heart disease is common, and up to half the cases of atrial fibrillation are now reported as idiopathic in various studies. This is a very high proportion if one recalls the classically limited proportion of 10% or so of so-called 'lone' atrial fibrillation.

The preceding considerations most probably explain why the value of beta-blockers is not recognized in the treatment of atrial fibrillation. It seems to go without saying that beta-blockers are indicated when the causal or favouring role of beta-adrenergic stimulation is operating, but not in the other situations. As an obvious but generally ignored consequence, the efficacy of beta-blockers will closely depend on the type of atrial fibrillation in the cohort of patients included in any study. The autonomic nervous system is involved in atrial fibrillation as in any arrhythmia, and we have called attention to its particular importance in the onset and modalities of the paroxysmal forms. The opposition between vagually-mediated and sympathetically-mediated paroxysmal atrial fibrillation is probably also too simplistic: in many cases the situation is more complex and preferably one should speak of autonomic imbalance, and/or hypersensitivity of the arrhythmogenic substrate. However, this notion has at least the merit of calling attention to the fact that one cannot ignore the role of the autonomic nervous systems, as was done for so long in cardiac arrhythmias in general. Clearly no paroxysmal atrial fibrillation can be controlled just by manipulating the autonomic nervous system, but the fact is that some patients cannot be controlled without the help of beta-blockers, whereas prescribing beta-blockers may make them worse. Discontinuing beta-blocking therapy is often sufficient to render a type I drug effective in a patient with recurrent paroxysmal idiopathic atrial fibrillation, because in this situation the favouring role of the vagal tone predominates. On the other hand, every time heart disease or heart failure is present, adding beta-blockers to the treatment may be helpful or even essential.

What is relatively easy to explore in recurrent paroxysmal atrial fibrillation, simply because of the repetition of the attacks, is more difficult to analyse in patients with persistent forms. Recurrent attacks provide an opportunity to refine the information about the circumstances of onset and to check various therapeutic approaches, whereas by definition the situation is different in persistent atrial fibrillation. We can only extrapolate from other conditions, and the presence or the absence of heart disease and heart failure is probably the most reliable indication of whether beta-blocking therapy has a chance to be beneficial, or is useless or even detrimental. It is remarkable that, in the patients of Plewan and co-workers, only 26 had no evidence of organic disease, whereas 102 had either coronary artery disease, cardiomyopathy or valve disease. Unfortunately
the authors did not try to correlate the particular efficacy of drugs in either group, but the 4 to 1 proportion of patients with heart disease probably explains why the recurrence rate of atrial fibrillation at 1 year was as low as 40%, an unusual level even using more powerful antiarrhythmics. It is not evident whether a correlation could be found between drug efficacy and heart rate, a notion that is important each time the autonomic nervous system is considered. For instance, in a recent study reporting on the efficacy of metoprolol on the maintenance of sinus rhythm after conversion[6], the distinction was interestingly between the 53% and the 37% relapse rates of patients with a baseline heart rate of less or more than 80 beats . min⁻¹, respectively, in comparison with patients receiving placebo (61 vs 56). The general relapse rate at 6 months in the study by Kühlkamp et al.[6] was 48%, a value that is more in agreement with the literature than in the Plewan study[5], but the proportion of organic heart disease is also in sharp contrast because in the former the proportion was 2 to 1 rather than 1 to 4.

The heart rate would seem to be the simplest and most reliable way of identifying not only the potential responders to beta-blockade but also of evaluating on an a posteriori basis the appropriateness of such therapy. This was repeatedly the case in our experience with adrenergically-mediated atrial tachyarrhythmias, but one could argue that a bias may exist with the sensitivity of the sino-atrial node to sympathetic innervation or circulating catecholamines in this context. However, this also applies to ventricular tachyarrhythmias when they are split into obviously adrenergically-dependent or apparently adrenergically-independent types, according to their own behaviour and their overall responsiveness to beta-blocking therapy[8][9]. For instance, studying a total of 19 patients with ventricular arrhythmias, 9 with a basically adrenergic and 10 with a basically non-adrenergic profile, the former not only responded better to beta-blockers, but the mean 24-h heart rate at baseline tended to be higher (78·5 ± 9·3 vs 74·7 ± 8·6) and the heart rate decrease on drug was significantly more marked: 19% vs 8% (P<0·01). Curiously but certainly not coincidentally, these proportions were the same as we observed when we compared the effect of beta-blockade in normal subjects or in patients with left ventricular hypertrophy with or without heart failure[10].

Clinicians as well as pharmacologists are usually unaware of the fact that the effect of beta-blockers on sinus rhythm not only depends on the nature of the beta-blocker itself[9] but on the overall patient’s status. In our experience with acebutolol[8] there was a clear contrast between the 9·5% heart rate decrease obtained in normals and the 18·1% and 19·1% decreases observed in patients with left ventricular hypertrophy and patients with heart failure, respectively. The explanation for this fact is certainly related, in part, to the amount of adrenergic stimulation and beta-adrenergic receptor sensitivity in these various situations, but it is certainly not unequivocal.

The recent study by Opthof et al.[10] nicely observed that heart failure decreases rather than increases the intrinsic sino-atrial rate. When one puts together these notions, the observation made by Kjekshus[11] of a positive correlation between the amount of bradycardia and the survival benefit provided by beta-blocking therapy becomes very coherent, despite a different explanation from the one initially proposed: bradycardia is probably not a factor of benefit in itself, but rather the marker that a benefit can be expected from the treatment in patients with myocardial dysfunction, and the more so depending on the degree of heart failure. The degree of benefit will depend on the degree of heart failure since greater adrenergic stimulation is operating. We do not have enough of this mode of reasoning in mind when managing cardiac arrhythmias.

The question then arises as to whether the sinus rate and its changes provoked by drugs with beta-blocking effects is a relevant marker of their beta-blocking power. This question is important with a drug with a supposed type III effect, because the prolongation of the plateau phase of automatic fibres is at least one of the mechanisms of bradycardia they induce[12]. The effect of dl-sotalol is ambiguous in this regard, and it should be recalled that the specific effect of beta-blockers is not really to slow the heart rate but to decrease it in proportion of the level of adrenergic stimulation. For instance, a trivial observation we had with nadolol[7] was that the percentage of heart rate decrease was twice as much in the daytime as at night (20% vs 10%) but that the change in the day-to-night ratio of the heart rate (1·25 in basic conditions and 1·10 on beta-blockade) did not depend on the dosage or on the drug used when we compared nadolol and propranolol. The situation is different, however, when a beta-blocker like acebutolol is used because its intrinsic adrenergic effect is responsible for a less marked bradycardic effect at night compared to during the day, so that the day-to-night ratio is less depressed by acebutolol than by propranolol or nadolol (1·15 vs 1·10)[8]. Amiodarone is well-known to slow the sinus rate but not to change the day-to-night ratio because of the absence of any competitive beta-blocking action even if the mechanism of some beta-inhibitory effect remains unclear. As regards sotalol, clearly its bradycardic
effect is partly, but not only, due to its beta-blocking properties. Our experience is that the effect of sotalol on the day-to-night ratio of heart rate is limited, weaker than that of pure beta-blockers thus contrasting with its whole bradycardic effect that is very marked.

The above considerations probably explain why it is not pertinent to speak of the efficacy or the inefficacy of beta-blockers in the prevention of atrial fibrillation as long as the preceding conditions have not been considered. Regardless of the role of the autonomic nervous system, drugs like sodium-channel blockers are effective in preventing atrial fibrillation, and the problem of their potentially deleterious effects is related to the underlying heart. Amiodarone is active whatever the impact of autonomic factors, and no matter what the myocardial situation it is neither arrhythmogenic nor cardiotoxic. The success of sotalol came from its relative absence of extracardiac adverse effects compared to amiodarone and despite arrhythmogenic potentials that to some extent gave credit to its type III properties with their potential benefit.

We naturally tend to think that in the majority of situations arrhythmogenic and antiarrhythmic properties of drugs are intrinsically linked. Amiodarone is the known exception to this general rule, and its extracardiac side effects are the reason why it cannot be considered ideal. On the other hand, this is not a sufficient reason to consider sotalol an adequate surrogate. At the low dosage of 160 mg . day $^{-1}$ used by Plewan et al. it provoked two cases of torsade de pointes, a limited toxic effect compared to the 3–5% proportion that can be observed at larger dosages. However, this is still two too many and once again gives the opportunity of stressing how much the notion of a corrected QT interval is pernicious and misused in the domain of pharmacological surveillance. These two cases of torsade de pointes were observed in patients with a QT duration of 550 and 580 ms in the context of a heart rate of 48 and 40/min, respectively. Therefore, the corrected QT values were of 492 and 475 ms, respectively, that is, less than the usually admitted dangerous limit of 500 ms. This clearly exemplifies how misleading it may be to compensate, ‘to correct’ and in fact to mask one favouring factor of torsade de pointes (the QT prolongation) by the other (the bradycardia).

We should be conscious of how biased we are in our method of evaluating the indications of drugs, the way we evaluate their mode of action and their effects as well as their potential hazards.

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References