Predictive value of atropine response in patients with bradyarrhythmia in the presence of bradycardic drugs

Valor predictivo de la respuesta a la atropina en pacientes con bradiarritmia en presencia de fármacos bradicardizantes

To the Editor,

As many as 21% of emergency department admissions for symptomatic bradycardia are for bradycardia in the presence of bradycardic drugs (BDs).[1] In these patients, the admissions are often prolonged and the interventions invasive (eg, temporary pacemakers, drugs such as isoprenaline). In this context, clinical practice guidelines recommend that physicians wait until the drugs are eliminated, which normally happens after 5 half-lives. However, the clearance rate depends on multiple factors, some of which are patient-specific (eg, age, weight, renal function)[2] and some of which depend on the bradycardic agent[3,4]; in addition, these conditions are generally relatively unpredictable. The management of patients with bradycardia in the presence of BDs is associated with a high rate of complications, prolonged hospitalizations, and, occasionally, unnecessary pacemaker implantation.10.1016/j.recesp.2022.04.003

The drug atropine acts by selectively antagonizing the muscarinic receptor in a net parasympatholytic effect. In the heart, atropine particularly affects the sinus node and atrioventricular (AV) node, increases heart rate, and improves AV conduction. Atropine has been used to treat symptomatic bradycardia in various contexts, such as in acute myocardial infarction and vagal situations, as well as in patients with bradycardia in the presence of BDs,[1] with acceptable results.

We postulated that the transient action of atropine in the context of bradycardia in the presence of BDs would have diagnostic utility in the early identification of patients who will maintain the pacemaker indication after the washout period, that is, patients with bradycardia in the presence of BDs and not those with bradycardia induced by these drugs.

Table 1
Characteristics of the patients studied based on the response to atropine and on pacemaker implantation.

Patients' characteristics	Negative response	Positive response	*P*
Patients	16	31	
Age, y	77.5 [74.8-83]	78.5 [73-81.8]	NS
Male sex	11 (68.5)	21 (67.7)	NS
Glomerular filtration rate, mL/min/1.73 m²	59.5 [38.8-77.5]	42.5 [28.8-64.7]	.18
Previous treatment			
Beta-blockers	13 (81.2)	26 (83.8)	NS
Digoxin	1 (6.2)	9 (29)	.074
Beta-blocker eye drops	2 (12.5)	1 (3.2)	NS
Nondihydropyridine calcium antagonists	0	2 (6.4)	NS
Time from last dose, h	12 [9-18]	12 [9.25-15]	NS
Electrocardiogram			
AVB/blocked AF	15 (93.7)	19 (61.2)	.025
Slow AF	1 (17.4)	8 (21.7)	NS
Sinus bradycardia	0	3 (21.7)	NS
Wide QRS	11 (68.7)	14 (45.2)	.157
Ventricular rate < 40 bpm	7 (43.7)	13 (41.9)	NS
Patients' characteristics by pacemaker implantation	**With pacemaker**	**Without pacemaker**	***P***
Patients	33	13	
Age, y	79 [75-83]	76 [72-80]	NS
Male sex	25 (75.7)	7 (53.8)	NS
Glomerular filtration rate, mL/min/1.73 m²	56 [38-76]	34 [16-60]	.059
Previous treatment			
Beta-blockers	28 (84.8)	11 (84.6)	NS
Digoxin	7 (21.2)	3 (23.1)	NS
Beta-blocker eye drops	3 (1)	0 (0)	NS
Time from last dose, h	12 [9-16]	12 [10-15]	NS
Electrocardiogram			
AVB/blocked AF	25 (75.2)	9 (69.2)	NS
Slow AF	5 (15.1)	4 (30.7)	NS
Sinus bradycardia	3 (4.3)	0	NS
Wide QRS	21 (63.6)	4 (30.7)	.045
Ventricular rate < 40 bpm	14 (42.4)	6 (46.1)	NS
Response to atropine			
Negative	16 (48.5)	0	.003
Positive avoid clashing	17 (51.5)	13 (100)	.003

AF, atrial fibrillation; AVB, atrioventricular block; NS, not significant.
Data are expressed as No. (%) or median [interquartile range].

Accordingly, we performed a prospective 1-year observational study (from January 2017 to January 2018) in a cohort of consecutive patients with bradycardia in the presence of BDs (beta-blockers, nondihydropyridine calcium antagonists, or digoxin) to determine the negative response (NR) rate to atropine and estimate its ability to predict pacemaker need. We excluded patients treated with any other type of antiarrhythmic drug and those who did not sign the informed consent form approved by the Ethics Committee of University Hospital of Nuestra Señora de Candelaria (Tenerife, Spain).

On arrival, patients underwent baseline electrocardiogram and electrocardiographic monitoring. Next, we administered 1 mg intravenous atropine, and a rhythm strip was recorded in the first 3 minutes and when changes occurred in the heart rate during monitoring, waiting up to 10 minutes after drug administration. Two types of responses were recorded: *a)* NR: no change in the sinus rate in the context of sinus bradycardia, no improvement in the degree of AV block, including blocked atrial fibrillation (AF), or no increase in the ventricular heart rate in patients with slow AF, and *b)* positive response: an increased sinus rate in patients with sinus bradycardia, normalization or improvement of AV conduction in the context of AV block, or an increased ventricular rate in patients with slow AF. Pacemaker implantation decisions were made independently of the test result at least 48 hours after the last dose; all patients discontinued negative chronotropic drugs from admission and did not restart them in the subsequent 3 months. Patients who received a pacemaker underwent a postdischarge visit (after 7-10 days) in which the programming parameters were optimized to prioritize AV conduction and the intrinsic sinus rate. At 3 months, we evaluated the pacing percentages in the chamber of interest (ventricular pacing in the case of AV block or AF and atrial pacing in the case of sinus bradycardia).

The study included 46 patients. Baseline characteristics are shown in table 1. A NR was seen in 16 patients (34.8%) and a pacemaker was implanted in 33 patients (71.7%). In total, 100% of patients with a NR required pacemaker implantation at 3 months (n = 16; 1 patient did not undergo implantation due to death during admission). In contrast, 51.5% of patients with a positive response ultimately received a pacemaker (n = 17) (P = .003). In addition, the type of response was the only independent predictor of pacemaker implantation (P = .009), after adjustment for other variables that were associated with pacemaker implantation before adjustment (glomerular filtration rate and wide QRS). Sensitivity, specificity, positive predictive, and negative predictive values were 41.2%, 66.6%, 58.3%, and 91% at the time of the test. At 3 months, the corresponding values were 38.9%, 68.7%, 58.3%, and 100%.

Of those who received a pacemaker, patients with a NR had a higher pacing percentage than patients with a positive response (94.4% vs 71.4%; P = .04).

The most pertinent datum from this series is that 100% of patients with a NR had a pacemaker indication and a high percentage of pacing in the first 3 months of follow-up. However, the data do not demonstrate the clinically relevant usefulness of a positive test result. This simple and safe test may eliminate the delay to implantation when patients attend the emergency department with bradycardia in the presence of BDs, as well as the possible complications and additional costs associated with longer hospitalizations. The results of this series support the value of a prospective and randomized assessment of the ability of the atropine test, together with that of other previously reported variables, to predict the need for pacemaker implantation in patients with bradycardia in the presence of BDs.[2]

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AUTHORS' CONTRIBUTIONS

L. Álvarez-Acosta is responsible for the initial idea for the study and its design and wrote the first draft of the manuscript. L. Anmad Shihadeh was in charge of data collection from patients, participated in the design, performed the statistical analysis, and revised the manuscript. L.I. Pérez-Méndez was in charge of the methodological supervision of the study, in addition to the statistical analysis and the correction of all versions of the manuscript. N. González was in charge of data collection from patients and participated in the design of the study and manuscript revision. P. Ruiz-Hernández helped with the design and the first draft of the manuscript, as well as the subsequent corrections. J. Hernández-Afonso participated in the study design, data analysis, and manuscript revision.

CONFLICTS OF INTEREST

None.

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