ATRIOVENTRICULAR BLOCK AFTER ADMINISTRATION OF ATROPINE IN PATIENTS FOLLOWING CARDIAC TRANSPLANTATION

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Abstract

Atropine is widely used as a parasympatholytic agent during diagnostic and therapeutic procedures. We observed an unexpected paradoxical response to atropine after cardiac transplantation.

In a study investigating the occurrence of autonomic reinnervation after cardiac transplantation, atropine, at 0.015 mg/kg body weight, was given intravenously to 23 patients (mean age, 56±8 years) 98 days to 6.4 years after transplantation.

Two patients experienced a witnessed syncope 40 and 150 min after administration of atropine. Second-degree atrioventricular (AV) block was documented in the first patient immediately afterward, and third-degree AV block was seen on 24-hr electrocardiogran monitoring in the second patient. A third patient developed documented AV block 15 min after atropine but experienced no sequelae because of a previously implanted pacemaker.

Although the underlying mechanism is not clear, these findings suggest that atropine may paradoxically cause high-degree AV block in patients after transplantation. Accordingly, it should be used with caution and appropriate monitoring in these patients.

We report on an unexpected adverse effect of atropine in three patients after cardiac allograft transplantation. Because atropine is frequently used during diagnostic or therapeutic procedures, we believe that this adverse effect should be brought to general attention.

In a study investigating the occurrence of autonomic reinnervation after cardiac transplantation, atropine, at 0.015 mg/kg body weight, was given intravenously to 23 patients (mean age, 56±8 years; 21 men and 2 women) 98 days to 6.4 years after transplantation (median, 679 days) to assess parasympathetic reinnervation. In addition, carotid sinus massage was performed. To assess sympathetic reinnervation, the heart rate response to a unilateral handgrip exercise (0.25 atm for 3 min) and tilt testing (80° for 10 min) was measured. Moreover, time domain of heart rate variability was analyzed by 24-hr electrocardiogram (ECG*) recordings (1). Studies were performed in the absence of graft rejection, as documented by endomyocardial biopsies. The project was approved by the local ethical committee and considered to be in accordance with ethical standards. Informed consent was given by all patients.

Data are presented as frequencies (percentage) or as mean ± SD. Group comparisons were performed using the Mann-Whitney *U* test. A *P*-value of less than 0.05 was considered statistically significant.

Three patients (13%) had a paradoxical response to atropine. Patient 1, a 46-year-old man who had received a transplant 5.7 years earlier, suffered from a clinically observed cardiac syncope lasting 15 sec that occurred 40 min after administration of atropine. Even though he was not monitored at that time, the ECG recorded immediately afterward showed second-degree atrioventricular (AV) block, which had never been observed before. After 2 hr, the AV block had completely disappeared and he remained free of any symptoms until he died 7 months later due to an intracerebral hemorrhage unrelated to his cardiac disease.

At 3.1 years after his transplantation, patient 2, a 60-year-old man, had an endocardial single-chamber permanent pacemaker (VVI) implanted early after transplantation because of symptomatic, intermittent, higher degree AV block. However, repeated ECGs during the second and third year after transplantation, as well as a Holter ECG in the course of this study, showed persistent sinus rhythm without AV block. Fifteen minutes after atropine administration, third-degree AV block occurred. The pacemaker promptly set in for 1 min, after which the AV block disappeared.

Patient 3, a 56-year-old woman, at 1.3 years after transplantation, suffered from a witnessed cardiac syncope outside of the hospital 2½ hr after the administration of atropine. She had never suffered from a syncope either before or after that event. In a 24-hr ECG before the event, a 4-sec episode of second-degree AV block was seen. This did not recur in a subsequent 24-hr [SDNN index], ECG, and no tachycardias could be documented.

All three patients had evidence of sympathetic reinnervation. All three showed only a slight decrease in heart rate during carotid sinus massage (2-3 beats/min), and only one of them had an increase of 5 beats/min in response to atropine. Nevertheless, parasympathetically influenced components of heart rate variability were greater in these three patients in comparison to the others (root mean square successive difference of successive RR intervals [r-MSSD], 16.9±2.8 msec vs. 11.2±5.6 msec, *P*=0.02; proportion of adjacent normal RR intervals >50 msec [pNN50],

1.8±1.1% vs. 0.9±2.4%, *P*=0.05; mean ± SD of successive 5-min RR intervals over 24 hr [SDNN index], 18.5±4.5 vs. 13.2±6.6, not significant).

There is no ready explanation for this unexpected effect of atropine after cardiac transplantation. So far, five different muscarinic receptors have been found, three of which mediate biochemical and physiological effects (M1, M2, and M3) (2). Of these, postsynaptic M2 receptors mediate parasympathetic effects in the heart (3, 4), and presynaptic M1 receptors may be involved in a short-loop negative feedback mechanism (5). This negative feedback mechanism requires intact parasympathetic innervation.

Atropine is used as a nonspecific parasympatholytic agent because its affinity to M1 receptors is only two to four times higher as compared with M2 receptors (6). However, a parasympathomimetic effect at very low dosages or during the first few minutes of administration has been described. Blockade of cerebral cholinergic M1 receptors by atropine has been suggested to cause this effect (7), but it was also found with parasympatholytic agents that do not pass the brain-blood barrier (8).

The three patients who, after cardiac transplantation, suffered from a higher degree AV block did not respond uniformly to our tests of parasympathetic function. Based on findings from the analysis of heart rate variability (higher pNN50 and r-MSSD), there is evidence that some degree of parasympathetic reinnervation occurred. Although every attempt at explanation must remain speculative, it is interesting to note that acetylcholine mediates parasympathetic as well as parasympatholytic effects in guinea pig atria by M2 receptors (9). If this were also true in patients after transplantation, the parasympathomimetic activity of atropine might explain the occurrence of high-degree AV block.

One could also speculate that the activity of pre- and postsynaptic muscarinic receptors recurs to a different extent during parasympathetic reinnervation. Given the higher affinity of atropine to presynaptic M1 receptors, this hypothesis could also explain our observations.

In addition, it has been hypothesized, based on findings in newborn versus adult animals, that postsynaptic M1 receptors as well as presynaptic sympathetic M1 receptors may be present in early stages of normal

development (10). Although obviously unproved, the stimulation of postsynaptic M1 receptors or the inhibition of a negative feedback mechanism of the sympathetic efferents by atropine during early stages of reinnervation might also explain the observed adverse effect.

Although we cannot explain the underlying mechanisms, it is noteworthy that 3 out of 23 patients responded with this clinically important adverse effect to atropine. Thus, the use of atropine for diagnostic or therapeutic procedures in patients after cardiac transplantation seems to require careful monitoring. Although the longest interval between administration of atropine and occurrence of AV block in our patients was 2½ hr, a somewhat longer observation period might be advisable.

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Footnotes

Abbreviations: AV, atrioventricular; ECG, electrocardiogram; pNN50, proportion of adjacent normal RR intervals >50 msec; r-MSSD, root mean square successive difference of successive RR intervals.

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