Effect of 5-fluorouracil on sinoatrial node and conduction system of heart

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ABSTRACT

Background: 5-FU a cytostatic agent is used to treat various malignancies. Cardiotoxicity is infrequent complication of 5-FU. Previously we had observed ECG changes in our patients on 5-FU viz sinus bradycardia, atrial fibrillation. We also found that 5-FU bradycardia might be a hypervagotonia as vagolytics abolished it. This study was undertaken to assess the impact of this commonly used chemotherapeutic agent on basic physiologic parameters of impulse initiation and conduction in human heart. The aim was to study effect of 5-FU on electrophysiological properties of SA node and conduction system of heart.

Methods: Pre -5FU state patients were subjected to electrophysiological study and following parameters were checked viz heart rate, CSNRT, SACT, AH and HV intervals and wenckebach point. Post 5- FU state these parameters were again checked. Response to Atropine was seen in patients who developed sinus bradycardia.

Results: Sinus bradycardia was seen in 8% (n=2) of patients in post 5FUstate Their electrophysiological parameters SNRT, CSNRT, SACT, AH were mildly prolonged (above the normal) in post 5FU state. Post atropine there was increase in heart rate and the deranged electrophysiological parameters came back to normal. Atrial fibrillation was seen in two patients while performing sinus nodal functions in post 5FU state.

Conclusions: Sinus bradycardia is a rare cardiotoxic side effect of 5FU, is a result of an autonomic imbalance viz hypervagotonia which is abolished by atropine and more common in infusin form than bolus. Infra-his conduction is not altered and threshold for inducing atrial arrhythmias is decreased in post 5-FU state.

Keywords: Atropine, Electrophysiology, 5-Flourouracil, Sinus bradycardia

INTRODUCTION

5-fluorouracil (5-FU) is a synthetic pyrimidine antimetabolite that is used as a cytostatic agent for various malignancies. 5-FU is relatively S-phase specific which potently inhibits thymidylate synthetase by competitive binding resulting in thymine depleted state ("thymine less death"). Cardiotoxicity is an infrequent complication of 5-fluorouracil chemotherapy. The incidence of 5-fluorouracil cardiotoxicity is reported to be in the range of 2.5 to 10%. It can manifest as angina, myocardial infarction, prinzmetal's angina, supraventricular arrhythmias and asymptomatic ST-T wave changes. Fluorouracil induced cardiotoxicity is more frequent during first cycle. Continuous intravenous infusion is reported to be more likely to cause cardiac events which are more probably due to increased intravenous volume administered. We observed some electrocardiographic changes in patients receiving 5-FU based chemotherapy viz sinus bradycardia, atria fibrillation etc. Though not exotic, these arrhythmias had been described in world literature on 5-FU cardiotoxicity. However, case reports and personal communications about similar arrhythmias...
resonated in the years to follow. We also found that 5-FU bradycardia might be a hypervagotonia as vagolytics would abolish it.\textsuperscript{11} This study was undertaken to assess the impact of this commonly used chemotherapeutic agent on basic physiologic parameters of impulse initiation and conduction in human heart.

**METHODS**

In this study we prospectively enrolled 25 patients irrespective of age, gender and ethnicity, who were under the oncology care of Sheri Kashmir Institute of Medical Sciences, Srinagar on the chemotherapy protocol that included 5-FU. Ethical committee of the Institute approved the study design. All those patients who were on 5-FU (infusion) for various malignancies and who had to receive first cycle of chemotherapy. Patients were included irrespective of type of underlying malignancy, age and sex. Patients were excluded if they had baseline electrocardiogram (ECG) abnormalities as defined in Minnesota code, concomitant use of other cardiotoxic drugs particularly anthracycline antibiotics, known case of structural heart disease, cardiac muscle disease or has an implanted cardiac device (Pacemaker or ICD), baseline dyselectromyias or arterial blood gas abnormalities at the time of study initiation, unless rapidly corrected, recent or past history of lower limb deep vein thrombosis, bleeding diathesis.

The 12 lead ECG (resting) was taken in all patients. ECG were scanned for any abnormalities in rate, rhythm, electrical axis, chamber hypertrophy, myocardial ischemia or infraction and repolarization abnormalities. All patients had normal ECG in accordance with minnesota code i.e. (minnesota code-normal -1-0-0). Complete blood counts were checked. Serum sodium: level of 135 to 145 meq/l was taken as normal. Serum potassium: level of 3.5 to 5.5 meq/l was taken as normal. Echocardiography was done in all patients for evaluation of valves, chamber size, wall thickness, wall motion abnormalities and ejection fraction on two-dimensional and M-mode echocardiography. After proper consent patient was transferred to cardiac cath lab where under all aseptic precautions a 6 French side arm sheath was inserted in right femoral vein. Using a decapolar catheter (EPcatheter) following E.P parameters were taken-heart rate (HR), sinus nodal recovery time (SNRT), corrected sinus nodal recovery time (CSNRT), sinoatrial conduction time (SACT), AH Interval, HV Interval, wenckebach point up to the rate of 180. After quick baseline EP parameter assessment, patient received 5-FU (dose and duration as defined by medical oncologist, infusion was given over 4 days). Following which same parameters were reviewed within 24 hours. In-patients who developed sinus bradycardia, response to atropine was assessed. 6 F sheath was removed and puncture site compressed till adequate clinical hemostasis was achieved. Patient received two doses of ceftrixozone 50mg per-kg-bodyweight before and after the study.

SNRT (sinus nodal recovery time) was recorded by pacing right atrium at rates progressively faster than sinus rate, which results in a delay in post pacing response. The duration from last paced beat to first sinus beat was taken as SNRT. Rapid stimulation of sinus node suppresses the intrinsic automaticity resulting in delay in post pacing response\textsuperscript{12}.CSNRT (corrected sinus nodal recovery time) was recorded by subtracting basal cycle length from SNRT.\textsuperscript{12} SACT (sinoatrial conduction time) was recorded by eight beat atrial stimulation (Narula method). Short trains of eight beats of slow atrial pacing at rates above the shortest cycle length.\textsuperscript{12} Wenckebach point was checked by doing rapid atrial pacing at rates of 110,120,140,160 up to 180. Normal value for these parameters were taken as SNRT Normal up to 1600 ms, CSNRT normal up to 525 ms.\textsuperscript{13}

SACT normal up to 206 ms, AH interval normal 60 to 125 ms, HV interval normal 35 to 55 ms.\textsuperscript{14} Ideal response to atropine was taken as greater than 15\% increase in heart rate.\textsuperscript{15}

Intragroup and intergroup comparisons were performed while applying students’ t test for statistical independence and paired comparison besides Chi-square, odds ratio and descriptive statistical analysis was possible with the help of SPSS±11.5

**RESULTS**

In this study 52\% (n = 13) were female and 48\% (n = 12) were male. The mean age for females was 45.8±4.86 years (range 28 to 60) and the mean age for males was 59.25±9.324 years (range 46 to 70). The overall mean age was 52.28±11.2 years (range 28 to 70). Maximum heart rate before receiving 5FU was 90 and minimum 68 (mean 76±7.55). After receiving drug maximum heart rate was 86 and minimum heart rate was 46(mean 66±11.23).

Sinus bradycardia was seen in 8\% (n = 2) of patients in post 5FUstate which was statistically insignificant (p >0.05). Both were male. It was seen in 16.6\% (n = 2) of male patients.

Heart rate in these two patients was 48 and 53 per minute compared to 70 and 72 per minute before receiving 5FU. Their electrophysiological parameters SNRT, CSNRT, SACT, AH were mildly prolonged (above the normal) whereas HV interval was normal in post 5FU state. Post atropine there was increase in heart rate to 100 and 96 per minute respectively and the deranged electrophysiological parameters SNRT, CSNRT, SACT, AH (Figure 1 and 2) came back to normal.

Also in these two patients wenckebach point was present at rapid atrial pacing rate of 140 (after drug) where as it was absent in them up to rapid atrial rate of 180 before they received 5-FU. Sinus bradycardia was seen in patients who were on continious intravenous infusion.
Atrial fibrillation was seen in two patients while performing sinus nodal functions in post 5FU state. One was reverted back to sinus rhythm by over drive pacing and another by pharmacological cardioversion. In rest of the patients all electrophysiological parameters (SNRT, CSNRT, SACT, AH, HV) were seen to be in normal range before and after receiving drug. In two patients sinus nodal function could not be performed in post 5FU state because of atrial fibrillation.

Figure 1: Post 5FU increase in corrected sinus nodal recovery time (CSNRT) with return to normal after atropine.

Figure 2: Post 5FU increase in AH interval with return to normal after atropine.

DISCUSSION

Earlier a study was conducted in our Institute where 24-hour Holter monitoring of patients on 5-Fluorouracil was done. One of the rare cardiotoxic event in that study was sinus bradycardia. We also noticed that 5-Fluorouracil induced bradycardia may be due to hypervagotonia? As vagolytics abolished it. Before attributing it to autonomic imbalance, more objective and scientific look in to sinus nodal functions was needed. Aziz S et al noticed that cardiotoxicity occurred during the inaugural cycle of 5-FU infusion in all five patients. All the patients in this study had supraventricular events, which is in accordance with other studies, but one patient developed sinus bradycardia which disappeared after atropine. This occurrence of sinus bradycardia is not often reported in literature and needs to be kept in mind while assessing cardiotoxicity of 5-FU.

The incidence of 5FU related sinus bradycardia in our study was 8% (n = 2). These patients had prolonged sinus nodal functions and AH interval. Post atropine their heart rate increased and the electrophysiological parameters SNRT, CSNRT, SACT, AH interval) came back to normal. This response of sinus bradycardia and electrophysiological parameters to atropine explains the role of hypervagotonia in 5FU related bradycardia which is further substantiated by the presence of Wenkebach point at rapid atrial pacing rate of 140 in these two patients (it was absent up to rapid atrial pacing rate of 180 before receiving 5FU).

Incidental atrial fibrillation was seen in two patients while performing their sinus nodal function in post 5FU. The absence of atrial fibrillation in these patients before receiving 5FU may explain the ease with which atrial fibrillation is inducible in post 5FU state and possibly a decreased threshold for inducing such arrhythmia.

Limitation of the study was that, the study sample in our study was small and only two patients developed bradycardia. So extrapolation of these results requires further validation with larger studies.

CONCLUSION

Sinus bradycardia is a rare cardiotoxic side effect of 5FU, is a result of an autonomic imbalance viz hypervagotonia which is abolished by atropine and more common in infusion form than bolus. Infra-his conduction is not altered and threshold for inducing atrial arrhythmias is decreased in post 5-FU state.

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