Gatifloxacin-induced prolongation of QT_C interval

Drug induced prolongation of corrected Q-T interval (QT_C) is increasingly being recognized as an adverse event associated with fluoroqinolones.[1] It has been shown that the radicle in position 5 of the fluoroquinolone ring is responsible for QT_C prolongation. Thus a proton (H^+) at this position is associated with QT_C prolongation by 3 ms as in gatifloxacin.[2]

Gatifloxacin is one of the commonly used antimicrobials for the lower respiratory tract infections and urinary tract infections in our setup for both indoor and outdoor patients. Its oral efficacy as well as once daily administration makes it an eminently suitable antimicrobial for home therapy. In view of this, we considered it worthwhile to study its effect on QT_C interval.

The study was conducted at Shri C.U.Shah Medical College and Hospital, Surendranagar. All patients admitted to medical wards or attending O.P.D and prescribed gatifloxacin for various clinically valid indications during the period of 2 months i.e. 1/11/2003 to 30/12/2003 were enrolled in the study. It was ensured that none of the selected patients received any other drug that may prolong Q-T interval. A base line 12-lead ECG was taken using an automated ECG machine (Maestro) prior to administration of gatifloxacin. Gatifloxacin was administered in the dose of 400 mg once in a day for 5 days. The 12 lead ECG was repeated on 5th day. Q-T interval from both ECGs (before and after gatifloxacin administration) was calculated manually (two physicians independently calculated Q-T and QT_C interval from these ECGs) and corrected according to the heart rate of the patients using Bezzet's formula (QT_C = Q-T interval / (R-R msec) $^{1/2}$ For calculation of Q-T and QT_c the lead showing longest Q-T interval was used [3] QT_C interval remains somewhat longer in females, so we have arbitrarily taken a QT_C interval of >0.47 sec in females and >0.45 sec in males as prolonged QT_C.[4] Patients were divided in two groups consisting of 14 patients showing normal QT_C interval and 6 patients showing prolonged QT_C interval. Intra group and inter group QTc values were compared employing paired and unpaired t-test respectively.

It is necessary to point out some limitations of our study at this juncture:

1. Limited sample size. (data collected over a pre decided period of two months).
2. Only one base line and one post drug 12 lead ECG has been taken in each case.
3. Timing of ECG does not necessarily correlate with the time at which maximum concentration of drug is likely to be present in the plasma.
4. Though electrolyte estimations (especially potassium) have not been done, none of the ECGs and clinical assessment of patients suggested any possibility of the electrolyte imbalance.

A total of 35 patients (including outdoor and indoor patients) were prescribed gatifloxacin for various indications during the period of study. Out of these 15 patients were not available for follow-up on 5th day of drug administration & hence were excluded from study. These were OPD patients. Though excluded from the study, percentage of patients showing prolonged QT_c after gatifloxacin were derived presuming that none of these fifteen developed prolongation of QT_c. Out of remaining 20 patients, 12 were males and 8 females. Of these, six females and eight males did not show QT_C interval prolongation. Group mean with SD of these 14 patients has been presented in part A of table 1. Four males and two females showed QT_C interval prolongation. This prolongation met both criteria i.e. in individual cases it was prolonged by 50 msec or more compared to baseline QT_C interval and exceeded the upperlimit of 0.45 seconds in males and 0.47 seconds in females.

For statistical analysis male and female patients were combined. So group A consists of total 14 patients who did not show QT_C interval prolongation as per selected criteria of the study. Comparison of QT_C interval before and after drug administration does not show statistically significant difference.

As opposed to this in group-B QT_C interval was prolonged to 0.520 seconds from base line value of 0.435 seconds. This shows statistically significant difference within the group by paired t test ($P<0.0025$). Comparison of QT_c value after gatifloxacin between groups A and B, by unpaired t-test also shows significant difference ($P<0.002$). [Table 1]

Table 1

Incidence of QT_c prolongation by gatifloxacin

Groups	*Total number of patients (n=20)*	*Mean age (yrs)*	*Mean QT_c interval (sec)*	
			before gatifloxacin	*after gatifloxacin*
A (QT_c not prolonged)	14	39.479±12.845	0.442±0.047	0.446±0.036
B (QT_c prolonged)	6	38.625±16.443	0.435±0.037	0.520±0.035

Values are mean±SD. *P<0.002 when compared to both before gatifloxacin (group B) and after gatifloxacin (group A).

Reported incidence of QT_C interval prolongation leading to "torsade de pointes"[5] indicates that levofloxacin and gatifloxacin have a fairly high propensity to cause this adverse effect while an older drug like ciprofloxacin is certainly much safer in this respect. The newer agents be it levofloxacin, gatifloxacin or sparfloxacin have much lower margin of safety and hence require very careful assessment of a patient before starting therapy.

Our results certainly corroborate reported high incidence with newer agents like gatifloxacin. QT_C interval prolongation in 6 out of 20 patients is definitely a high incidence. Fortunately none of these patients developed any cardiac complications. 3 of 6 patients did not have any risk factors known to produce QT_C interval prolongation. Out of remaining three one was 70 year old and two others had ECG evidence of ischemic heart disease with normal base line QT_c interval. This points to the fact that in normal population 8-10% of patients may get QT_C interval prolongation with administration of usual therapeutic dose of gatifloxacin i.e.400 mg per day (if our sample represents the general population).

An interesting finding of our study is QT_C interval prolongation in two female patients less than 40 years old without any known risk factor.

If we consider known cardiac actions of chloroquine; this raises the possibility of an interaction between gatifloxacin and chloroquine. Both may produce QT_C interval prolongation and the combination therefore is likely to have an additive action. Our limited literature search could not find any report of this kind or any possible explanation for the phenomenon except the one- that we have suggested i.e. additive pharmacological action on myocardium of chloroquine with gatifloxacin resulting in prolongation of QT_c interval.

To sum up we feel that widespread use of newer fluoroquinolones is not desirable and requires very careful patient assessment by the clinician.

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References

1. Satoh Y, Sugiyama A, Chiba K, Tamura K, Hashimoto K. QT-prolonging effect of sparfloxacin, a fluoroquinolone antibiotic assessed in the in vivo canine model with monophasic action potential monitoring. J Cardiovas Pharmacol 2000;36:5105.
2. Lannini PB ,Tillotson GS. Evaluating the risk of cardiac toxicity. Pharmacotherapy 2001;21:261-2.
3. Wagner GS, editor. Marriot's Practical Electrocardiography.9th ed. New Delhi, India: B.I. Waverly Pvt. Ltd; 1994.
4. Mirvis DM, Goldberg AL. Electocardiography. In : Zipes DP, Libby P, Bonow RO, Braunwald E, editors. Braunwald's Heart Disease- A textbook of cardiovascular medicine, 7th ed. USA: Elsevier Saunders; 2004. p.118-
5. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. Pharmacotherapy 2001; 21:1468-72.