

Is prolongation of the QTc interval during isoflurane anaesthesia more prominent in women pretreated with anthracyclines for breast cancer?[†]

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Background. Inhalation anaesthetics and anthracycline chemotherapeutic drugs may both prolong the QT interval of the electrocardiogram. We investigated whether isoflurane may induce or augment QTc prolongation in patients who had previously received cancer chemotherapy including anthracycline drugs.

Methods. Forty women undergoing surgery for breast cancer were included in the study. They were divided into two groups: (A) women previously treated with anthracyclines ($n=20$); and (B) women not treated with antineoplastic drugs ($n=20$). All patients received a standardized balanced anaesthetic in which isoflurane 0.5 vol% was used. The QT and corrected QT intervals were measured before anaesthesia, after induction and tracheal intubation, after 1, 5, 15, 30, 60 and 90 min of anaesthesia, and during recovery.

Results. In both groups we observed a tendency to QTc prolongation, but statistically significant differences among baseline values and values observed during isoflurane-containing anaesthesia were seen only in group A. During anaesthesia, significant differences in QTc values between the two groups were observed.

Conclusion. In female patients pretreated with anthracyclines for breast cancer, the tendency to QTc prolongation during isoflurane-containing general anaesthesia was more strongly expressed than in patients without previous chemotherapy.

Br J Anaesth 2004; **92**: 658–61

Keywords: anaesthesia, general; anaesthetics volatile, isoflurane; chemotherapy, anticancer; monitoring, electrocardiography, QT interval; pharmacology, anthracyclines

Accepted for publication: December 7, 2003

The QT interval of the electrocardiogram reflects the period from the start of ventricular depolarization to the onset of ventricular repolarization. Its prolongation is associated with arrhythmias, such as polymorphic ventricular tachycardia (torsade de pointes) and ventricular fibrillation.^{1,2} Prolongation of the QT interval may be congenital (congenital long QT syndrome), concurrent with morphological and functional abnormalities as a part of various syndromes (e.g. Jervell and Lange-Nielsen syndrome, Romano–Ward syndrome).^{3,4} Acquired prolonged QT interval may also be observed in cases of electrolyte imbalance (hypokalaemia, hypocalcaemia, hypomagnesaemia), and secondary to drug treatment (group I and III anti-arrhythmics, selected antibacterial agents, antihistamines, antidepressants, etc.).¹ Recipients of anthracycline antibiotics, administered as part

of cancer chemotherapy regimens, may also have prolonged QT intervals: prolongation of the QT interval is one of the markers of postanthracycline cardiotoxicity^{5,6} and its intensity is related to the overall dose of administered anthracyclines.⁷

Drugs administered in anaesthesia have diverse effects on the QT interval, some prolonging it (e.g. thiopental, isoflurane, sufentanil)^{8–11} and others shortening it (e.g. propofol, halothane)^{8–12} or not influencing the length of the QT interval (e.g. etomidate, vecuronium, diazepam, midazolam).^{8,9} The combination of two or more agents

[†]This study was presented in part at the Euroanaesthesia 2003 Meeting, Glasgow, UK, May 31 to June 3, 2003 [*Eur J Anaesth* 2003; **20** (Suppl. 30): 126; Abstract 480].

prolonging the QT interval is believed to increase the risk of arrhythmia development.¹ Therefore, we aimed to analyse the effect of isoflurane, a potent inhalation anaesthetic known to prolong the QT interval, on the QT interval of patients previously treated with anthracyclines.

Material and methods

Approval of the institutional research and ethics committee was obtained for the study. Forty women aged 45–60 yr (ASA physical status I–II), scheduled for breast cancer surgery, were enrolled in the study. Equal numbers of patients were allocated to group A if they had previously received anthracycline-based neoadjuvant chemotherapy and to group B if they had not received such treatment.

Patients were excluded if they were receiving Vaughan-Williams class 1 or 3 anti-arrhythmics, if they had a history of heart disease or circulatory insufficiency, or if they were receiving psychotropic or other drugs known to prolong the QT interval. Patients with preoperative electrolyte abnormalities were also excluded, as were those who had a significant arrhythmia or conduction disturbance on their preoperative ECG (excepting four patients in group A with postanthracycline prolongation of QTc interval).

Anaesthetic management was standardized for all patients. They received estazolam 2 mg p.o during the evening before surgery and midazolam 0.1–0.2 mg kg⁻¹ p.o. 1 h before surgery. Before induction of anaesthesia with etomidate 0.2 mg kg⁻¹, fentanyl 1–2 µg kg⁻¹ and vecuronium 0.1 mg kg⁻¹, all patients breathed oxygen spontaneously through a facemask. After tracheal intubation, the patients' lungs were ventilated mechanically using the ADU S/5™ (Datex Ohmeda, Bromma, Sweden) anaesthesia system. A fresh gas mixture of nitrous oxide/oxygen, 2:1 ratio, 3 litres min⁻¹, was used and the inspired concentration of isoflurane was adjusted to maintain an end-tidal concentration at 0.5 vol% (Aladin™ vaporizer; Datex Ohmeda). During anaesthesia, further doses of fentanyl and vecuronium were given as required. As part of standard non-invasive monitoring, the ECG was recorded with the Agilent Page Writer M1170A ECG device (Agilent Technologies, Andover, MA, USA). QT and QTc measurements were performed automatically (an option of the ECG device), and verified manually according to Malik and Batchvarov.¹³ The QT interval was measured in lead II of the ECG, and the correction was calculated according to Bazzet's formula ($QTc = QT RR^{-1/2}$). Measurements were performed before anaesthesia, before and after tracheal intubation, and subsequently after 1, 5, 15, 30, 60 and 90 min of anaesthesia with isoflurane and after emerging from anaesthesia. QTc values greater than 0.44 s were considered to be prolonged, based on reports by Khan¹ and Wisely and Sipton.⁸

The minimum group size of 18 was calculated in order to achieve a study power of 90% with type I error rate (alpha) of 0.05. For the purposes of the calculation, we used values

of the QTc interval (range, mean, standard deviation) from the study of Benhorin and colleagues.¹⁴

The data are presented as mean (SD). Statistica 6.0 (Polish version) was used for statistical calculations. The data were tested for normality using the Shapiro–Wilk test. Statistical analysis of group differences was performed using Student's *t*-test with Bonferroni correction. The differences within groups were analysed using analysis of variance for repeated measurements. Homoscedascity was verified with Levene's test and significant differences were analysed with Fisher's *post hoc* LSD test. $P < 0.05$ was considered to be significant, and $P < 0.0011$ was considered to be significant when a Bonferroni correction was used.

Results

Most patients in group A had received adriamycin as their anthracycline; 18 patients followed the FAC regimen [5-fluorouracil, doxorubicin (adriamycin), cyclophosphamide]. Six of these patients received six cycles of adriamycin, one patient received five cycles, two patients received four cycles and 11 received three cycles. The total dose of adriamycin ranged from 180 to 600 mg (mean 270 mg, SD 127.2 mg) or 150–300 mg m⁻² body surface area (mean 202.78 mg m⁻², SD 67.46 mg m⁻²). The remaining two patients in group A were given three cycles of epirubicin in the FEC regimen (5-fluorouracil, epirubicin, cyclophosphamide). They both received a total dose of anthracycline of 150 mg m⁻² body surface area. The mean time from the last administered dose of anthracycline to the time of surgery and our study was 33.1 days (SD 26.68 days).

The patients' ages, body mass and height and the duration of anaesthesia were similar in the two groups (Table 1). Patey radical mastectomy was the surgical procedure used for all patients.

A comparison of the corrected QT values recorded in the two groups is presented in Table 2. After induction of anaesthesia, a decrease in QTc was observed in both groups, followed by an increase after tracheal intubation. The addition of isoflurane to the inspired gas mixture caused a statistically significant prolongation of the QTc interval only in group A. Significant differences in QTc values between the two groups were observed at 5, 15, 30 and 90 min of isoflurane anaesthesia.

Table 3 summarizes the number of patients in whom the QTc value exceeded the reference value of 0.44 s during the

Table 1 Characteristics of the patients. Mean (SD or range)

	Group A	Group B
Number of patients	20	20
Age (yr)	52.2 (46–60)	52.8 (45–60)
Height (cm)	161.7 (5.6)	162.5 (4.6)
Body weight (kg)	69.75 (14.7)	74.8 (15.9)
Duration of anaesthesia (min)	142.5 (41.4)	156.4 (36.9)

course of the study. This phenomenon was observed almost exclusively in group A. The only ventricular arrhythmia to be observed was an incidental ventricular extrasystole, of no haemodynamic significance, which occurred in one patient in group A.

There were no significant differences in mean heart rate between the groups, the mean (SD) ranging from 59.55 (9.74) to 78.45 (18.75) beats min^{-1} in group A and from 55.1 (9.74) to 79.05 (16.93) beats min^{-1} in group B. A significant difference was found between the baseline values of mean arterial pressure (MAP), which was 101.07 (11.76) mm Hg in group A and 92.88 (10.86) mm Hg in group B ($P < 0.05$). This difference did not persist after induction of anaesthesia, when the average MAP ranged from 86.8 (12.69) to 112.38 (20.8) mm Hg in group A and from 86.33 (10.97) to 102.9 (12.82) mm Hg in group B.

Discussion

The main finding of our study is that patients who have received anthracycline-based chemotherapy are more prone to prolongation of the QTc interval during administration of isoflurane than those who have not. Although QTc prolongation is a marker of postanthracycline cardiotoxicity,^{7 15} we did not observe a statistically significant difference in QTc values between our groups before anaesthesia. Group comparisons at most other time points, however, showed statistically significant prolongation of the QTc interval in women pretreated with anthracyclines. Furthermore, QTc values increased from baseline only in the patients who had received anthracyclines. As more than 50% of the

anthracycline-pretreated women (compared with a single patient in the control group) developed prolongation of the QTc interval above the upper normal limit of 0.44 s, it is reasonable to conclude that anticancer chemotherapy with anthracyclines makes patients sensitive to the potential arrhythmogenic action of isoflurane.

Although the QTc interval exceeded 0.44 s in more than 50% of patients pretreated with anthracyclines, no serious arrhythmias were observed. This finding is in line with other reports of QTc prolongation after administration of various anaesthetics.^{11 12 16 17} It would appear that the risk of arrhythmias is low unless a QTc value of 0.6 s is exceeded;^{1 18} we did not observe such long QTc intervals in any patient. It should be emphasized that higher isoflurane concentrations than those used in our study may enhance QTc prolongation towards 0.6 s in women given anthracycline chemotherapy.

Other authors have observed a statistically significant prolongation of the QTc interval in healthy subjects inhaling isoflurane.^{12 16} In these studies, however, inhalational agents were administered during induction of anaesthesia, whereas we used drugs that do not influence the QTc interval. We also used relatively low concentrations of isoflurane and our patients had received midazolam for premedication, which can reduce QTc prolongation induced by other anaesthetics.¹⁶

Acknowledgements

The authors wish to thank the nurses of our department for their assistance during the study; special thanks are due to Mrs Michalina Szczukowska, Mrs Edyta Wojcik and Mr Piotr Holajn.

Table 2 Changes in QTc interval in groups A and B. Data are mean (SD). * $P < 0.05$ within the group, compared with baseline; ** $P < 0.01$ within the group, compared with baseline; #Student's *t*-test; ##significant with Bonferroni correction

	Baseline	After induction	After intubation	Duration of anaesthesia with isoflurane (min)						After recovery from anaesthesia
				1	5	15	30	60	90	
Group A	0.410 (0.028)	0.389* (0.029)	0.418 (0.029)	0.400 (0.031)	0.429* (0.049)	0.423 (0.027)	0.429* (0.034)	0.434** (0.040)	0.435** (0.034)	0.402 (0.031)
Group B	0.391 (0.023)	0.382 (0.024)	0.394 (0.031)	0.376** (0.026)	0.386 (0.018)	0.388 (0.029)	0.395 (0.02)	0.401 (0.015)	0.398 (0.022)	0.399 (0.02)
Intergroup comparison#	$P < 0.05$	n.s.	$P < 0.05$	$P < 0.01$	$P < 0.001^{##}$	$P < 0.001^{##}$	$P < 0.001^{##}$	$P < 0.01$	$P < 0.001^{##}$	n.s.

Table 3 Number of patients with QTc > 0.44 s

	Baseline	After induction	After intubation	Duration of anaesthesia with isoflurane (min)						After recovery from anaesthesia
				1	5	15	30	60	90	
Group A	4	0	3	2	8	8	11	9	11	4
Group B	0	0	0	0	0	1	0	0	0	0

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