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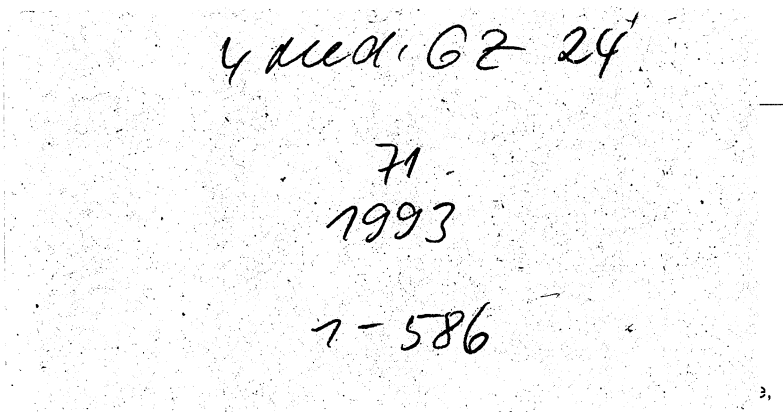

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Contents of Volume 71

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No 4: pp 257– 338 published April 1, 1993
No 5: pp 339– 420 published May 3, 1993
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Clinical Pharmacology Original Article

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Chronic pentamidine aerosol prophylaxis does not induce QT prolongation*

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Summary. Intravenous administration of pentamidine is known to cause long-QT syndrome (Torsade de pointes tachycardias and large QT prolongation) in rare cases and to cause small QT prolongation regulary. A similar pattern is seen with other drugs known to cause a long-QT syndrome. Pentamidine aerosol prophylaxis is commonly used to prevent *Pneumocystis carinii* pneumonia in HIV-infected persons. The goal of this study was to clarify whether pentamidine aerosol prophylaxis induces QT prolongation. We examined 100 patients receiving pentamidine aerosol prophylaxis at a rather high dose (300 mg biweekly) for at least 1 month (range 1–24) by determinating the QT interval corrected for heart rate (QTc), blind for treatment. In a cross-sectional study, QTc was not different in 50 HIV-infected patients with chronic pentamidine aerosol prophylaxis (413 ms), 50 similar HIV-infected patients without pentamidine (407 ms), and 50 similar patients without HIV-infection and without pentamidine (407 ms). In a longitudinal study in another 50 HIV-infected patients, QTc was the same before (414 ms) and on long-term (median 9-month) pentamidine aerosol prophylaxis (414 ms). In contrast to the case with intravenous pentamidine, we found no QT prolongation and thereby no risk of long-QT syndrome with pentamidine aerosol prophylaxis.

Key words: Pentamidine – Arrhythmias – QT interval – Long-QT syndrome

In persons infected with the human immunodeficiency virus (HIV) pentamidine aerosol prophylaxis (PAP) effectively reduces the risk of *Pneumocystis carinii* pneumonia (PcP) [11]. A rare, little-known, but life-threatening adverse effect of systemic pentamidine therapy is long-QT syndrome (LQTS), the combination of QT prolongation (with a heart rate-corrected QT – or QTc – usually longer than 480 ms) and ventricular tachycardias (usually of Torsade de pointes type). We know of a total of 14 published cases since 1987 [2, 5, 7, 12, 14–18, 20]. All cases were treated for PcP with the usual doses of pentamidine intravenously or intramuscularly for 6–20 days. The patients were young men (median age 33 years) without renal insufficiency, heart disease, or previous arrhythmias. At the first occurrence of LQTS none was treated with other drugs known to induce LQTS. QT prolongation prior to pentamidine therapy was found in two cases, hypokalemia in six and hypomagnesia in six. In at least seven cases ventricular tachycardias occurred without any of these predisposing conditions. Electrical or mechanical defibrillation was necessary in at least seven cases. Tachycardias did occur, at the latest 2 days after discontinuation of pentamidine, and QTc usually became normal within 1 week. In one case intravenous pentamidine was successfully substituted by pentamidine inhalations [15].

The risk of PAP inducing LQTS needs to be established for the following reasons: (a) A causal relationship of systemic pentamidine therapy to LQTS is now very likely. (b) LQTS due to pentamidine may not be dose related but rather an "idiosyncratic" reaction [3]. (c) One case of acquired immunodeficiency syndrome (AIDS) and LQTS during PAP (among other possible factors) has been reported [8]. (d) Other systemic adverse effects of systemic pentamidine treatment have also been reported on PAP [9, 10, 13]. (e) Although inhaled pentamidine is absorbed only minimally [4–6], accumulation in human myocardium with chronic PAP has not been excluded. (f) A rare but life-threatening adverse effect (LQTS) lowers the benefit-risk ratio more for a prophylactic measure (PAP) than for an effective systemic treatment of

Abbreviations: AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; LQTS = long-QT syndrome; PAP = pentamidine aerosol prophylaxis; PcP = *Pneumocystis carinii* pneumonia; QTc = QT interval, corrected for heart rate

* Dedicated to Prof. Dr. N. Zöllner on the occasion of his 70th birthday

a life-threatening disease (PcP). (g) PAP use is much more common compared to systemic pentamidine treatment of PcP. (h) If a PAP-related risk of LQTS exists, it can probably be reduced by adequate precautions. (i) Inhaled pentamidine is an alternative regime to systemic treatment in a subgroup of patients with PcP [1].

Counting cases of LQTS during PAP seems to be an inacceptable, slow method to establish the risk of this rare adverse effect. One estimate of the risk of a drug inducing LQTS may be the incidence of large QT prolongation. Thus, systemic pentamidine therapy at an ususal dose induced a QTc prolongation longer than 480 ms in 1 of 10 cases [3], in 10 of 32 cases [17], and in 2 of 12 cases [19]. Comparison of QTc prior to and during treatment by paired but blind comparison may be a more sensitive method. With this method, systemic pentamidine induced a small but statistically significant QT prolongation of 30 ms (SD 32 ms, $P<0.01$) even in a small number of cases ($n=12$) [19].

Patients and methods

At our institution PAP was introduced in 1988 using pentamidine isoethionate (Pentacarinat) 300 mg biweekly. This is half the usual interval or twice the usual dose. Salbutamol (Sultanol, 0.7 mg) was inhaled simultanously to prevent bronchospasm and cough.

Study design

The study consisted of two parts. In a cross-sectional study the ECGs of 50 patients on chronic PAP (having no ECG prior to PAP) were compared with the ECGs of two control groups without PAP, one group of HIV-positive, and one group of HIV-negative subjects. In a longitudinal prospective study the ECGs of 50 patients prior to and during PAP were compared. The study started in July 1989.

Cross-sectional study

An ECG was performed in 50 HIV-positive patients on chronic PAP (at least 4 weeks, at least three inhalations). For each of these 50 cases a similar HIV-positive subject without previous or current PAP (HIV-positive control) and a similar patient without any indication of HIV-infection (HIV-negative control) were selected, having (a) sinus rhythm and no bundle branch block, (b) similar heart rate (± 10 beats/min), (c) similar age (± 3 years), and (d) the same sex. For some cases a control fulfilling all four criteria could not be found; these cases were not excluded but a control as similar as possible selected. In addition, we matched cases and HIV-positive controls in terms of disease severity of the HIV-infection as far as was possible. We excluded patients having specific reasons for an ECG such as known or suspected cardiac disease, severe hypertension, hypokalemia, and treatment with cardiovascular drugs.

Longitudinal study

In a prospective study of another 50 patients an ECG was performed prior to the start of PAP and at least once during chronic PAP for at least 4 weeks. For the total group, the last ECG before and the last ECG during PAP was compared. A subgroup analysis was carried out in terms of to the duration of chronic PAP (see Table 4). In addition, in 16 of these cases the ECG was performed immediately prior to and 30 min after the first inhalation of pentamidine plus salbutamol. For this group 13 volunteers also studied before and after the inhalation of salbutamol (without pentamidine) served as controls.

Measurements

A 12-lead routine ECG with a paper speed of 50 mm/s and a rhythm strip of 2 min was used. The QT interval was measured twice and QTc (Bazett formula) was calculated. In the cross-sectional study, all ECG measurements were performed blinded for treatment group. In the longitudinal study the ECGs were measured pairwise per patient, but blinded for treatment. We used Student's *t*-test for paired and unpaired comparisons.

Results

Cross-sectional study

The patients with PAP were nonselected except for the exclusion of one patient with bundle branch block. The group means for age and heart rate were very similar in the three groups (see Table 1). Despite the intention to select HIV-positive controls with similar disease severity (as HIV-positive cases), there were only 23 HIV-positive controls with AIDS as compared to 37 in the HIV-positive case group ($P=0.004$ by χ^2 test; see Table 1). The average QTc was minimally longer in the group of HIV-positive cases (with PAP) as compared to the HIV-positive controls and the HIV-negative

Table 1. Patient characteristics

	PAP	*n*	Mean age (years)	Mean heart rate	No. of AIDS cases
Cross-sectional study					
HIV-positive cases	+	50	40.6	79.9	37
HIV-positive controls	−	50	40.5	80.0	23
HIV-negative controls	−	50	41.0	79.0	0
Longitudinal study					
HIV-positive cases	−/+	50	40.2	83.1	37

Table 2. QTc values (ms) in the cross-sectional study ($n=50$)

		Mean	SD	Range
HIV-positive cases	(PAP +)	413	23	350–484
HIV-positive controls	(PAP −)	407	21	362–452
HIV-negative controls	(PAP −)	407	22	357–447

controls (see Table 2). This difference was not statistically significant by unpaired or by paired comparison ($P>0.05$). In subgroups of patients with AIDS with or without PAP QTc values did not differ. Gross QT prolongation longer than 480 ms was seen in one case with PAP (484 ms) and in no control (see range in Table 2). QTc prolongation longer than an upper normal limit of 440 ms was seen in five cases with PAP (including the one with 484 ms), in three HIV-positive controls and in two HIV-negative controls.

Longitudinal study

Of the 50 patients 37 had AIDS before PAP, very similar to the 36 of 50 cases with PAP in the cross-sectional study. Since the mean values of heart rate and age were also similar (see Table 1), no patient participated in both studies, and QTc was measured by the same method and the same persons, the patients of the longitudinal study before PAP may be seen as the best control group for the cases in the cross-sectional study. QTc was nearly identical in cases with PAP in the cross-sectional study (mean 413 ms) and in cases before PAP in the longitudinal study (414 ms). Comparing the last ECG before and the last ECG obtained during chronic PAP, QTc remained unchanged for the total group of 50 patients. Heart rate, PQ and QRS duration also did not change (see Table 3). The T waveform remained unchanged with PAP. A QTc longer than 480 ms was not seen in this series; a QTc longer than 440 ms was found in seven cases before and in six cases during chronic PAP.

Table 3. ECG results in the longitudinal study ($n=50$)

	Before PAP	During PAP	Difference[a]	SD
Heart rate (beats/min)	83.1	83.1	0.0	15.1
PQ time (ms)	161	163	+2	11.0
QRS time (ms)	85	86	+1	6.5
QTc time (ms)	414	414	0	22.0

[a] Differences nonsignificant

Table 4. QTc results (ms) in the longitudinal study

	Duration	*n*	QTc before PAP	QTc during PAP	Difference	SD
Acute studies						
Control		13	402	402	0	13
PAP	1×	16	412	415	+3	11
Chronic studies						
PAP	1 month	17	422	414	−8	17
PAP	2–5 months	18	413	418	+4	18
PAP	6–12 months	20	411	411	0	18
PAP	13–24 months	15	406	407	+1	31

In four subgroups of ECGs according to duration of chronic PAP, there was no significant change in QTc in any group and no tendency toward QT prolongation with time (see Table 4). After the first inhalation of pentamidine plus salbutamol QTc was not significantly prolonged (as compared to QTc prior to inhalation and as compared to the change of QTc in the control group; see Table 4). In 44 patients with 2-min rhythm strips there were a total of four single ventricular extrasystoles (in three patients) prior to PAP and the same number during PAP.

Discussion

PAP did not induce QTc prolongation in a large number of patients ($n=100$) with prolonged treatment (up to 2 years) using twice the usual dose (300 mg biweekly). This is in contrast to systemic pentamidine therapy, in which a statistically significant QTc prolongation of 30 ms was found in a rather small number of patients ($n=12$) using the same measurement of QT blind for treatment [19]. QTc was prolonged neither in the single-dose studies (around the time of the expected peak plasma concentration of pentamidine [4, 6]) nor after chronic PAP (6–24 months in 35 cases, since slow accumulation in myocardial tissue is not definitely

excluded despite low systemic absorption of inhaled pentamidine). Therefore, a false-negative result, i.e., undetected QT prolongation by PAP, seems very unlikely.

So far we have tested four drugs known to induce LQTS, with a similar method. All four drugs (systemic pentamidine, prenylamine, terodiline, and sotalol) induced a small but statistically significant ($P<0.01$) prolongation of QTc (by 30, 29, 18, and 39 ms) in rather small groups of 12–18 nonselected patients ([19] and unpublished results). The method used proved to be sensitive for detecting a drug-related risk of a LQTS. Other indicators for an arrhythmogenic effect of PAP such as increased number of premature ventricular contractions, recurrent syncopes, and sudden unexpected death were not seen in this study or in other patients on PAP at our institution.

Except for the case described above [8], we have found no cases of AIDS and LQTS during PAP in the literature. However, we have heard of two cases with AIDS and LQTS without pentamidine and without known cause. We have seen one case with AIDS, reversible QTc prolongation up to 550 ms, and reversible cardiac enlargement. QTc prolongation (520 ms) appeared shortly before cardiac enlargement, was not drug related, and was probably caused by AIDS-associated myocarditis.

In conclusion, the risk of PAP inducing LQTS seems negligible.

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Subject Index of Volume 71