Amiodarone and chronic lung fibrosis

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Summary: A covariate analysis was performed on the major lung function indices that are affected by pulmonary fibrosis in 29 patients who had recently started amiodarone therapy and compared with those of a group of 41 patients who had been treated for a mean of 19.6 months. Patients with other factors which affect gas transfer were excluded. A trend towards reduction in transfer factor, transfer coefficient and membrane diffusion was detected but did not reach statistical significance. A lower than expected incidence of acute pulmonary fibrosis was observed. In the treated group, there was no deterioration of transfer factor, transfer coefficient or membrane diffusion with either increasing duration of therapy or total dose taken.

Introduction

Since 1980 there have been several reports of acute and subacute lung fibrosis and pneumonitis occurring in patients taking amiodarone (Marchlinski *et al.*, 1982; Suarez *et al.*, 1983). Holt *et al.* (1983) have shown that in patients taking amiodarone the native drug and its major metabolite desmethyl-amiodarone are found in highest concentration in the liver and second highest concentration in the lung. Kudenchuk *et al.* (1983) have suggested that amiodarone given for a mean of 5.6 months causes falls in transfer factor (TLCO) and total lung capacity (TLC) which are not always associated with symptoms. These changes were more likely to occur in those with a significantly low TLCO at the start of the study. Further, Greene *et al.* (1982) have reported that after 6 months treatment with amiodarone, TLC significantly decreased and diffusion capacity fell by 15% in nearly half the patients. This study examines whether long term treatment with amiodarone is related to low grade or chronic pulmonary fibrosis.

Methods

Initially, 126 patients who had been on long term amiodarone therapy and 67 patients who were within 8 weeks of starting amiodarone were randomly selected and a full range of lung function tests were performed. The case notes of all these patients were

examined and patients were excluded if they had any of the following factors which affect TLCO or its subdivisions: mitral or aortic valve disease, right to left shunt, left ventricular failure (past or present), pulmonary hypertension, thyrotoxicosis, sarcoidosis and previous lobectomy or pneumonectomy. Patients with all the following factors were considered to have emphysema and were also excluded: significantly elevated TLC and significant reductions of forced expiratory volume in one second/forced vital capacity (FEV₁/FVC), TLCO, transfer coefficient (KCO), and $\dot{V}_{\max}$ 60 and 75. Any factor was considered to be elevated or reduced if it was more than 20% higher or lower than its predicted value. Patients with haemodynamically insignificant mitral valve prolapse were accepted. All patients were of European descent. After these exclusions there remained a group of 41 patients (28 male) on long term amiodarone (group 1) and 29 patients (19 male) who had recently started treatment (group 2). The range of duration of treatment in group 1 was 5–47 months (mean 19.6 months) while that for group 2 was 0–7 weeks (mean 1.7 weeks).

The following lung function data were collected in each individual: FEV₁, FVC, residual volume (RV), TLC, expiratory flow volume loop, TLCO, transfer coefficient (KCO), membrane diffusion (DM), capillary volume (VC), capillary haemoglobin and blood gas analysis. DM and VC were calculated using the standard formula: $1/\text{TLCO} = 1/\text{DM} + 1/\theta\text{VC}$ after TLCO had been measured at high (86%) and low (14%) oxygen concentrations (where θ is the rate of reaction of carbon monoxide with haemoglobin) as described in Cotes (1979). Helium

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was used at 14% and carbon monoxide at 0.28%. All other measurements were made using standard techniques. The equipment used was the same for each patient and was standardized daily.

The values of TLCO, KCO, DM and VC were all corrected for haemoglobin concentration. Because the measurement of these 4 variables is sometimes unreliable, the coefficient of variation for each of these was calculated by making 10 measurements in 9 individuals on separate days at the same time each day and using the standard formula as found in Colton (1974): coefficient of variation = (s.d./mean) $\times$ 100% where s.d. and mean refer to each individual's 10 results.

Transfer factor and its subdivisions, TLC and PO_2 are known to be variously affected by age, sex, height, smoking habit and (sometimes) weight (Cotes, 1979). These 5 factors and the length of time for which each patient had been taking amiodarone were included in the comparison of groups 1 and 2 by means of an analysis of covariance using the SPSS computer program (Nei *et al.*, 1975). Using the same program, a multiple regression analysis was performed on group 1 subjects to determine whether increasing duration of therapy or total dose taken was associated with reductions in transfer factor or its subdivisions.

Results

The mean and range of coefficients of variation for TLCO, KCO, DM and VC are given in Table I. The results of lung function tests adjusted for those covariates found to be significant ($P < 0.05$) are summarized in Table II. Relative to group 2, DM was reduced in group 1 and the difference was significant only at the 10% level. There were also reductions in PO_2 , TLCO and KCO in group 1 compared to group 2 but none of these reached significance even at the 10% level. In group 1 only 2 values of KCO were more than 20% below their predicted and in each case this was only marginally so (predicted KCO 4.9, measured KCO 3.9; and predicted KCO 5.0, measured KCO 3.7). In neither case was there any clinical evidence of lung fibrosis. In group 2 however there were no significant falls in KCO.

Table I Mean and range of coefficients of variation for transfer factor and its subdivisions

	TLCO	KCO	DM	VC
Mean	5.15%	5.16%	18.6%	15.6%
Range	3.43 – 6.20	2.84 – 8.67	12.1 – 47.9	9.7 – 19.7

Table II Mean and standard deviation of lung function tests adjusted for significant covariates

Factor (units)	Group 1 (n = 41)	Group 2 (n = 29)	Significance (P value)
PO_2 (kPa)	9.70 (1.1)	10.0 (1.2)	0.146
TLC (l)	6.07 (1.5)	5.90 (1.12)	0.853
TLCO (mmol/min/kPa)	27.6 (7.4)	28.0 (6.0)	0.133
KCO (mmol/min/kPa/l)	5.04 (0.94)	5.29 (0.96)	0.113
DM (mmol/min/kPa)	41.0 (14.4)	43.8 (10.8)	0.063
VC (ml)	91.8 (33.7)	83.0 (27.0)	0.537

Neither TLCO nor any of its subdivisions were significantly reduced with increasing duration of therapy or increasing total dose of amiodarone, nor was TLC affected. Indeed the only significant finding in this analysis was that TLCO increased with increasing duration of therapy.

Discussion

As can be seen in Table I, there is a narrow range of coefficients of variation for both TLCO and KCO and the mean of this range is acceptable. However, for both DM and VC there was a wide scatter of coefficients of variation, the lowest of which is higher than the worst value for either TLCO or KCO. This would suggest that no firm conclusions can be drawn from the results of DM and VC but more reliance should be placed on TLCO and KCO which are shown to be reliable and repeatable tests.

Kudenchuk *et al.* (1983), who found a high incidence of significant falls in TLCO (associated with chest radiographic and usually symptomatic deterioration) in those who had a low TLCO before amiodarone therapy, make no reference to excluding patients with conditions like mitral valve disease or emphysema, which could be responsible both for the initial low value and for its subsequent fall. Similarly Greene *et al.* (1982) have not excluded such patients. It could therefore be argued that other factors are causing the observed effects in these patients. Our results do not confirm any strong statistical relationships between amiodarone therapy and reductions in TLC, TLCO or its subdivisions although there may be a trend in that direction. (As far as DM is concerned, such a trend could easily arise as a consequence of its high coefficient of variation.) This is despite the fact that our average treatment period is considerably longer than theirs. Further, we have not shown any

clinically significant falls in KCO since the noted falls in DM have been partially compensated for by a rise in VC in group 1.

Since the observed effect in the multiple regression analysis of a significant rise in TLCO with increasing duration of therapy in the treated group was not confirmed by the comparison of groups 1 and 2, this finding must be regarded with suspicion and no firm conclusion may be drawn.

It must be remembered that this study is not a straightforward comparison of lung function values between two different groups of people since the covariate analysis has corrected for differences in age, sex, height, weight and smoking habits between the groups. Of the 193 patients initially seen in the study, there was not a single case of acute pulmonary fibrosis. This represents an incidence of acute pulmonary fibrosis due to amiodarone much lower than has recently been suggested by Marchlinski *et al.* (1982).

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Conclusion

Our results do not support the thesis that long term amiodarone therapy causes low grade pulmonary fibrosis. Although there may be a trend towards that effect, it does not appear to be clinically significant in most cases. The observed incidence of acute pulmonary fibrosis was less than previously reported. The results of previous reports showing significant falls in TLC and TLCO must be regarded with some caution since patients with other factors which can affect transfer factor were not excluded from these studies.

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