Adverse reactions during treatment with amiodarone hydrochloride

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Abstract

Amiodarone was administered to 80 patients with recurrent cardiac tachyarrhythmias previously resistant to drug treatment. Forty nine patients were treated for ventricular tachycardia or fibrillation and 31 for supraventricular arrhythmias. The mean duration of treatment with amiodarone was 14·8 months (range six days to 51 months), permitting a total of 100 patient years of observation. Adverse reactions were observed in 69 patients. Severe side effects were encountered in 13: four patients developed interstitial pneumonitis, four patients developed incessant ventricular tachycardia, three patients taking amiodarone and digoxin sustained sinus node arrest with depression of escape foci, one patient developed hepatitis, and one patient developed hypercalcaemia with renal failure. Furthermore, a rise in the serum concentration of digoxin and potentiation of warfarin anticoagulation occurred in cases in which these agents were combined with amiodarone. Amiodarone was stopped in 14 patients because of side effects.

Although amiodarone is effective in suppressing arrhythmias in most patients in whom extensive use of antiarrhythmic drugs has been unsuccessful, it is associated with diverse and serious toxicity. These observations suggest that at present the use of amiodarone should be reserved for patients with life threatening or seriously disabling arrhythmias in whom longer established drugs have been ineffective or are contraindicated.

Introduction

Amiodarone hydrochloride has been in clinical use for 20 years and is effective in the treatment of angina pectoris and cardiac tachyarrhythmias.[1] Although certain adverse effects of amiodarone have been recognised for many years, it has been stated that such adverse reactions rarely necessitate stopping treatment.[2] Indeed, because of its efficacy and safety amiodarone has been suggested as an ideal antiarrhythmic agent.[3] Reports of serious adverse reactions during treatment with amiodarone, however, have recently been published.[4-12] Little detailed information exists on the incidence and nature of adverse reactions encountered during long term use of the drug in a large population of patients. We examined the adverse responses observed when amiodarone was administered to 80 consecutive patients at this hospital.

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Patients and methods

PATIENTS

Treatment with amiodarone was begun between 1978 and early 1982 in 80 patients who had been referred to the cardiac electrophysiology unit for management of refractory cardiac arrhythmias. The patients comprised 55 men and 25 women whose mean age was 60 (range 26-76). The arrhythmias being treated were recurrent sustained ventricular tachycardia (34 patients), ventricular fibrillation (10), symptomatic ventricular tachycardia that was not sustained (five), recurrent atrial flutter or fibrillation (15), and other supraventricular arrhythmias (16). The principal cardiac diagnoses in the patients were: atherosclerotic heart disease, 47 patients; no structural heart disease, 13; mitral valve prolapse, seven; the Wolff-Parkinson-White syndrome, five; cardiomyopathy, five; rheumatic heart disease, one; valvular heart disease, one; and congenital heart disease, one. Many patients had diminished left ventricular function; the mean resting left ventricular ejection fraction in patients presenting with ventricular tachycardia or fibrillation was 32% (range 9-65%). All patients had failed to respond to or had not tolerated a mean of 5·6 (range 3-10) antiarrhythmic drugs before receiving amiodarone.

Informed written consent was obtained from each patient before the start of treatment. Eye examination and thyroid and liver function tests were performed to give baseline values, and treatment with amiodarone was then started with constant electrocardiographic monitoring. A loading dose of 600-1200 mg daily was administered for an average of 16 days (range 5-48 days). In those patients whose prior arrhythmias had not caused haemodynamic instability, the daily dose of amiodarone was then reduced to 400 mg or less unless arrhythmias recurred, when the minimum dose necessary to control the arrhythmias was given. In patients with infrequent arrhythmias programmed cardiac stimulation was performed while they were not taking any antiarrhythmic drugs. They were then loaded with amiodarone alone, and electrophysiological testing was repeated once evidence of an effect of amiodarone on electrophysiological variables—for example, the QTc interval—was apparent. Patients in whom the induced arrhythmia was suppressed or who required more aggressive stimulation to induce the arrhythmia were discharged taking an empirically selected maintenance dose of amiodarone. If ventricular tachycardia was as readily or more easily inducible a second antiarrhythmic agent was added to amiodarone or the patient was discharged taking amiodarone alone in the expectation that it would have a delayed protective effect. Nine patients with ventricular tachycardia induced by programmed cardiac stimulation were discharged from hospital despite failure to ameliorate an inducible arrhythmia; their outcome has been reported previously.[13]

The average maintenance dose of amiodarone administered was 365 (SD 195) mg (range 100-1200 mg) daily in patients treated for longer than three months. Forty seven patients took other cardioactive drugs in addition during the study: 34 took digoxin for cardiac failure or to slow the ventricular response during atrial arrhythmias; nine took beta adrenergic blocking agents for hypertension or angina; and 15 took other antiarrhythmic agents.

FOLLOW UP EVALUATIONS

After being discharged from hospital all patients were seen initially every three months and subsequently every six months by one of us. Patients were encouraged to report any adverse reaction to their doctors and were seen and assessed within 24 hours of such an occurrence. At each routine follow up visit physical examination, slit lamp examination of the eye, and thyroid and liver function tests were performed in addition to routine biochemical and haematological studies. Patients were questioned at each visit about possible side effects. In the later stages of the study a chest x ray film was obtained routinely as part of the follow up assessment. Serum amiodarone concentrations were not measured during the study. Adverse reactions

are not reported here if in our opinion they might have been attributable to another drug or to any cause other than administration of amiodarone. The mean duration of treatment with amiodarone was 14·8 months (range six days to 51 months), representing a total of 100 patient years of observation.

INTERPRETATION OF DATA

None of the 80 patients was lost to follow up during the study. To assess the effect of dose on specific adverse reactions two way frequency tables were constructed with patients divided according to whether they received under or over 600 mg, the upper limit of the manufacturers' recommended daily dosage. Analysis was performed with the BMDP program (department of biomathematics, University of California), in which the χ^2 test, with Yates's correction if necessary, or Fisher's exact test is used as appropriate to measure the association of variables. Similar statistical techniques were used to examine the influence of digoxin on the incidence of the common adverse reactions as grouped in table I, and three way frequency tables were constructed to permit assessment of a possible interaction between amiodarone at high or conventional dosage and digoxin in the genesis of the common adverse reactions. Sufficient data were not available to permit a similar analysis of the less common adverse effects. Results are expressed as means and 1SD.

Results

Adverse reactions were noted in 66 patients (82%) during treatment with amiodarone (table I). Many of these side effects were tolerable, and some were dose dependent; in 14 patients (18%), however, amiodarone had to be stopped because of side effects that were considered to be intolerable by the patients or their doctors (table II). Amiodarone was withdrawn in an additional seven patients because of recurrent spontaneous arrhythmias and in eight patients because it failed to ameliorate induced arrhythmias. In all, 70 patients were discharged from the hospital taking amiodarone: 39 were being treated for ventricular arrhythmias and 31 for supraventricular arrhythmias. Eight patients with histories of ventricular tachyarrhythmias (20%) died suddenly after a mean of $10·6 \pm 11·4$ months' treatment with amiodarone. Ventricular fibrillation was documented as the terminal event in four of these eight patients. Seven non-sudden deaths occurred during the study. Recurrent symptomatic arrhythmias were noted in an additional 18 patients after dose reductions effected either as part of the routine regimen or because of adverse reactions. Amiodarone was continued in these patients because the frequency of arrhythmia was reduced, because addition of a second antiarrhythmic agent was helpful, or if a higher maintenance dose could be tolerated.

TABLE I—*Side effects of amiodarone*

	No of patients		No of patients
Neurological (n = 19; 24%):		Dermatological (n = 11; 14%):	
Ataxia	10	Photosensitivity	7
Dizziness	8	Blue-grey skin discoloration	3
Tremor	8	Urticaria (transient)	1
Headache	2		
Nightmares	2	Miscellaneous (n = 14; 18%):	
		Liver*	14
Gastrointestinal (n = 27; 34%):		Hair loss	2
Nausea	19	Visual disturbance	2
Anorexia	6	Hyperhydrosis	2
Diarrhoea	3		
Constipation	3	Neuromuscular (n = 11; 14%):	
Abdominal Pain	1	Generalised weakness	8
Epigastric burning	1	Proximal muscle weakness	5
Bitter taste	1	Muscle tenderness	1

*Increased activity of alanine aminotransferase and lactic dehydrogenase.

TABLE II—*Side effects necessitating withdrawal of amiodarone*

	No of patients	Mean duration (and range) of treatment (months)	Mean daily dose (and range) for 3 months before withdrawal (mg)
Interstitial pneumonitis	4	14 (3-36)	550 (400-1000)
Aggravation of ventricular tachycardia	4	0·65 (0·25-1)	800 (400-1200)
Nausea, vomiting, or anorexia	3	2·6 (2-3)	280 (242-400)
Profound muscle weakness	2	12·5 (8-17)	300 (200-400)
Hypercalcaemia	1	4	360

LUNG TOXICITY

Four patients (5%) treated with amiodarone developed clinical and radiological features consistent with interstitial pneumonitis; 59 had been taking amiodarone for over two months, giving an incidence in this group of 7%. Two of the patients were receiving amiodarone for recurrent, refractory supraventricular arrhythmias in association with the Wolff-Parkinson-White syndrome, one for recurrent atrial flutter, and one for recurrent ventricular tachycardia. The dose of amiodarone was 1 g daily in one patient and 400 mg daily in the three other patients, for three, 12, five and 36 months respectively. In two of the four patients the maintenance dose has been less than 400 mg but recurrent arrhythmias had necessitated reinstituting a daily dose of 400 mg. All four patients noticed gradually worsening dyspnoea, two complained of dry cough, and one had pleuritic chest pain in addition to dyspnoea.

Pulmonary function tests showed restrictive defects with reduced diffusing capacities. All patients were hypoxaemic with a mean oxygen tension at presentation of 9·4 (range 7·6-11·6) kPa (70·7 (range 57-87) mm Hg). There was bilateral opacification on the chest *x* ray film in each case (fig 1). Two of the patients were admitted to hospital with an initial diagnosis of cardiogenic pulmonary oedema but failed to respond to treatment with diuretics. A transbronchial lung biopsy specimen was obtained in one patient (fig 2), which showed a diffusely thickened hypercellular interstitium with alveolar exudation and fibrosis. No evidence of an infectious process was found in any of the four patients.

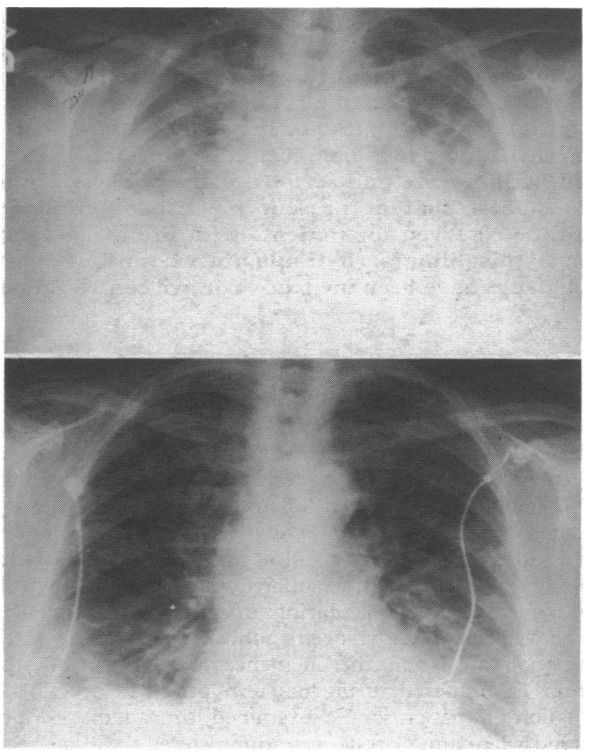

FIG 1—Chest *x* ray film before (top) and two weeks after withdrawal of amiodarone and start of steroid treatment.

As no other explanation of these findings could be found amiodarone was stopped in each case; the symptoms and *x* ray findings gradually resolved over the next two to eight weeks. Results of pulmonary function tests improved but were not within the normal range in two of the four patients three and six months after withdrawal of amiodarone. Although results of pulmonary function tests performed before amiodarone was started were not available for comparison, none of

these patients had had histories or symptoms of lung disease before starting amiodarone. Prednisone 80 mg daily was started in one patient who had severe dyspnoea and impairment of gas transfer (oxygen tension 7·6 kPa (57 mm Hg)) and may have contributed to the resolution of the lung disease. Two of the four patients were taking digoxin and one metoprolol in addition to amiodarone, and one was receiving amiodarone alone.

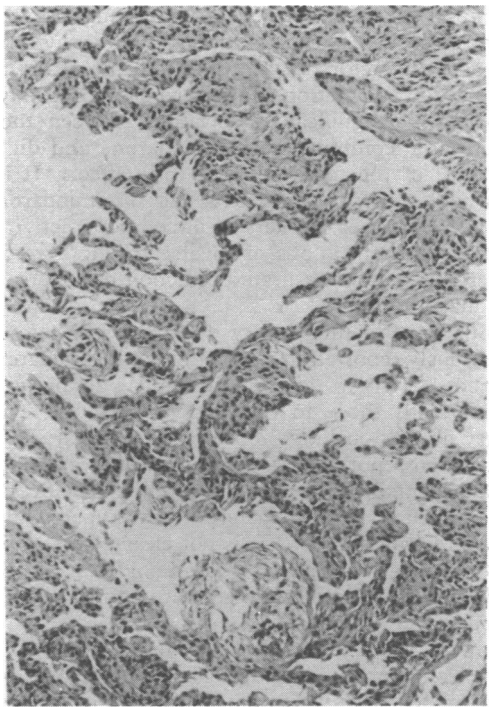

FIG 2—Transbronchial lung biopsy specimen obtained in patient whose chest *x* ray film is given in fig 1, showing hypercellular thickened interstitium with fibrosis and alveolar exudation. Hyperplastic pneumocytes and chronic inflammatory cells are prominent. (Haematoxylin and eosin ×150 (original magnification).)

DISTURBANCE OF CONDUCTION SYSTEM

Three patients developed sinus node arrest with depression of escape foci after a mean of 30 (range 7-42) days' treatment. Cardiac pacing was necessary in each case. The doses of amiodarone used were 600, 800, and 1000 mg daily. All three patients were taking digoxin in addition to amiodarone, and one patient was also being treated with a beta adrenergic receptor blocking agent. The serum digoxin concentration was at the upper end of the normal laboratory range in one patient and was not recorded in the two other patients when sinus arrest occurred. Subsequently, however, with similar doses of digoxin and amiodarone, the serum digoxin concentrations remained within the normal laboratory range for this hospital and no extracardiac evidence of digoxin toxicity occurred. Intracardiac electrophysiological studies performed on these patients before the introduction of amiodarone had shown normal sinus node function by overdrive pacing but prolonged His-Purkinje conduction times. Two of these three cases have been described in detail elsewhere.[7] All three patients continued to take amiodarone but with permanent cardiac pacing, as no other therapeutic options were available.

In a fourth patient first degree atrioventricular block progressed to Mobitz type I block after six days of treatment with amiodarone alone, 1200 mg daily.

INTRACTABLE VENTRICULAR ARRHYTHMIAS

Incessant ventricular tachycardia developed in four patients (5%) being treated for recurrent ventricular tachycardia after seven, 11, 30, and 35 days of treatment with amiodarone. Three of the four patients were taking digoxin, but amiodarone was the sole antiarrhythmic drug being taken; the mean dose used was 800 mg (range 400-1200 mg) daily. All four patients suffered numerous episodes of ventricular tachycardia with only minutes to a few hours between episodes. This contrasted greatly with the sporadic occurrence of ventricular tachycardia when they were not taking antiarrhythmic drugs or were taking antiarrhythmic drugs other than amiodarone. These tachycardias were only partly responsive to parenteral antiarrhythmic treatment that had previously been successful. Amiodarone was withdrawn in each case, and in three of the four patients the ventricular tachycardia gradually subsided over a period of time (24 hours to five days) that was directly related to the duration of treatment with amiodarone. One patient, in whom near constant ventricular tachycardia resulted in haemodynamic collapse, underwent emergency map guided aneurysmectomy, which successfully abolished his arrhythmia. Serum digoxin concentrations in the three patients receiving digoxin were 2·5, 0·4, and 0·9 μg/l, and the QTc intervals were 490, 470, and 440 ms respectively at the time that ventricular tachycardia recurred (the corresponding QTc interval in the patient not taking digoxin was 530 ms). Alternative treatment was started after amiodarone was withdrawn, and incessant ventricular tachycardia did not recur.

OTHER ADVERSE RESPONSES

Table I lists the more common, though less serious, adverse responses observed. These side effects of amiodarone have been described by other investigators[6 12 13]; although they were tolerated by many patients, amiodarone was stopped in five patients because of one or more of these reactions. Reducing the daily dosage of amiodarone improved or abolished symptoms in 19 of the 50 patients in whom this was attempted, but the underlying arrhythmia recurred in 15 of these 50 patients. There was no significant difference in the incidence of these adverse responses in patients maintained on more or less than 600 mg daily. Similarly, the simultaneous administration of digoxin could not be shown to contribute to the incidence of these symptoms in patients taking higher or lower doses of amiodarone.

Keratopathy[14] was observed in all patients who took amiodarone for longer than six months. Visual disturbances (halo vision) were reported by two patients but did not necessitate withdrawal of amiodarone. The free thyroxine index rose from 32 ± 8 μmol/l ($2{\cdot}5 \pm 0{\cdot}6$ mg/100 ml) to 41 ± 10 μmol/l ($3{\cdot}2 \pm 0{\cdot}8$ mg/100 ml), and rises in the mean triiodothyronine resin uptake and concentrations of reverse triiodothyronine similar to the findings reported by Melmed *et al*[15] were found; these values varied considerably between patients. Only one patient, however, developed clinical evidence of thyroid abnormality in this series, being treated for hypothyroidism after three years of treatment with amiodarone. Dermatological abnormalities—namely, photosensitive rashes and skin discoloration similar to those reported previously[16 17]—were found in 11 patients (14%). Eight of the 32 patients (25%) treated with amiodarone for over six months had moderate or severe photosensitive reactions necessitating avoidance of direct sunlight when possible and occasional dose reductions. Sun screens containing para-amniobenzoic acid may have afforded some protection in individual patients.

One patient who had been taking amiodarone 400 mg and digoxin daily for 12 weeks presented with symptomatic hypercalcaemia, hyperphosphataemia, and worsening of mild chronic renal failure (fig 3). Extensive laboratory investigations failed to explain these findings. Amiodarone was withdrawn and serum calcium and phosphate concentrations returned to normal over two weeks with resolution of symptoms. Renal function improved. Amiodarone was reintroduced at a dose of 200 mg daily and serum calcium, phosphate, and creatinine concentrations rose again. After final withdrawal of amiodarone the patient gradually became asymptomatic and laboratory variables again returned towards baseline values. One year later the patient was well; serum calcium and phosphate concentrations were normal, but serum creatinine concentrations remained higher than they had been before amiodarone was given.

Increases in serum activity of alanine aminotransferase and lactic dehydrogenase by more than 50% were seen in 14 out of 35 patients (40%) for whom adequate data were available, although in four patients the activities of these enzymes declined with continued treatment. One patient who had been taking amiodarone 800 mg daily for 20 months for recurrent ventricular tachycardia presented with gradually worsening malaise, fever, and abdominal tenderness. The liver was enlarged, tender, and palpable 6 cm below the costal margin. Serum bilirubin concentration was normal, serum alanine aminotransferase activity was 457 U/ml, lactic dehydrogenase activity was

297 U/ml, and alkaline phosphatase activity was 55 IU/l. No evidence of viral hepatitis was detected serologically. Liver biopsy was not performed. Symptoms and clinical and laboratory findings resolved after amiodarone was withheld. Subsequently, ventricular tachycardia recurred and amiodarone was reintroduced at 400 mg daily as no other treatment was indicated. Liver enzyme activities rose again, although to lower values than previously, and the patient remained asymptomatic. After taking the reduced dose of amiodarone for four months the patient collapsed and was found to be in ventricular fibrillation from which he could not be resuscitated.

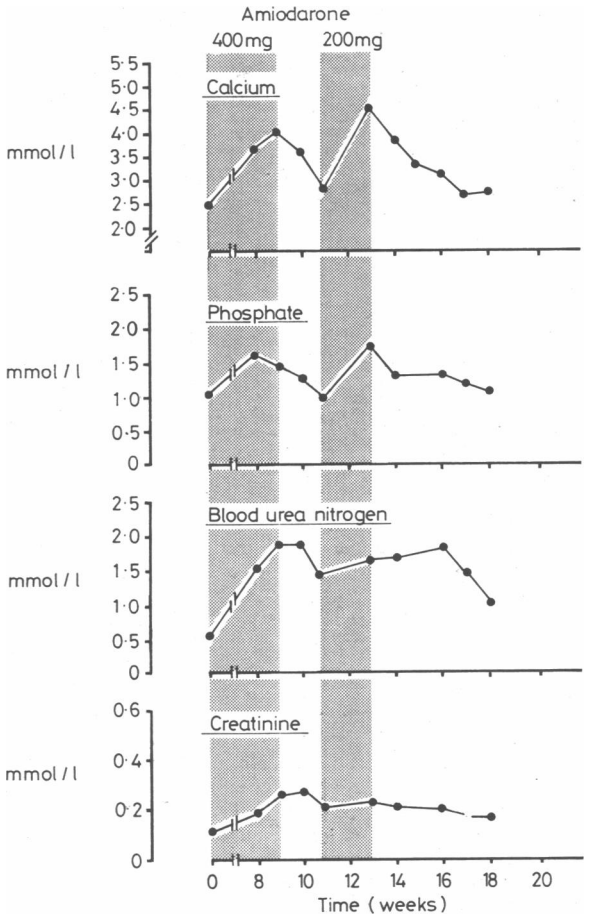

FIG 3—Sequential serum concentrations of calcium, phosphate, blood urea nitrogen, and creatinine. Rechallenge with amiodarone confirmed the associations.

Conversion: SI to traditional units—Calcium 1 mmol/l ≈ 4 mg/100 ml. Phosphate: 1 mmol/l ≈ 3·1 mg/100 ml. Blood urea nitrogen: 1 mmol/l ≈ 2·8 mg/100 ml. Creatinine: 1 mmol/l ≈ 11·31 mg/100 ml.

DRUG INTERACTIONS

Potentiation of the effect of warfarin was noted when warfarin and amiodarone were taken together. In two cases anticoagulation was reversed rapidly by administration of vitamin K. Lower doses of digoxin were used in patients in whom serum digoxin concentrations rose after the introduction of amiodarone.

Discussion

Amiodarone is highly effective against a wide range of cardiac arrhythmias. Its potential usefulness is limited, however, by frequent and potentially serious toxicity. The incidence, variety, and severity of adverse reactions found in this group of patients were greater than those in other reported series: amiodarone was withdrawn because of toxicity in 18% of our patients, compared with none in some series[20] and 15% in a series reported by Ward *et al.*[14]

We wondered whether the higher doses used or the concomitant use of digitalis and other drugs might account for the high incidence of adverse responses. Although some of the adverse reactions were improved or abolished by reducing the dose, many reactions occurred at the minimum dose required to control arrhythmias. Furthermore, the lack of efficacy of amiodarone in some patients even at the doses used is emphasised by the incidence of sudden death and recurrent arrhythmia,which were more common in this series than in previously reported groups. The incidence of adverse responses may therefore depend in part on the severity of the underlying arrhythmias and the extent of previous administration of antiarrhythmic drugs, in so far as these factors may be determinants of the minimum effective dose of amiodarone. Furthermore, three way analysis failed to show a significant association between the dose of amiodarone, the combination of amiodarone and digoxin, and the incidence of the more common side effects. It is not yet known whether serum concentrations of amiodarone or its metabolites,[21] or other markers of amiodarone activity such as raised serum concentrations of reverse triiodothyronine,[15] will permit early and more accurate prediction of adverse reactions in individual patients.

The four cases of lung injury that occurred were similar to those previously reported in association with amiodarone.[5 6 8–10] One patient,[9] with *x* ray findings and pulmonary function comparable with those in our patients, had no evidence of pulmonary fibrosis on lung biopsy or at necropsy. Diffuse lung injury has been reported in association with a growing number of chemical agents, with typical, though non-specific, findings of interstitial pneumonitis characterised by hypercellularity and varying degrees of fibrosis.[22] It is not clear whether direct lung toxicity or damage mediated by immunological mechanisms is responsible in the case of amiodarone or other drugs similarly implicated.

Marchlinski *et al* found no evidence of deposition of immunoglobulins, complement, or fibrinogen in lung biopsy material from two patients, but lysosomes distended with osmophilic granular material were found in macrophages, type II pneumocytes, interstitial cells, and endothelial cells.[23] Of particular concern are the findings of Greene *et al*,[24] who studied prospectively the effects of amiodarone on pulmonary function in a large number of patients. After six months' treatment at a mean dose of 560 mg daily 21% of their patients showed a greater than 15% decrease in total lung capacity, and diffusing capacity was reduced by at least 15% in 34% of the patients. These findings suggest a direct toxic effect of amiodarone and if confirmed by others will necessitate reassessment of the role of amiodarone treatment. Corticosteroids may speed resolution of symptoms and limit the extent of collagen formation. The presence of fibrosis in some of the reported cases, however, suggests that permanent lung damage may have occurred, since reversal of lung fibrosis in man has not been shown.

Amiodarone has a strong direct negative chronotropic effect when infused selectively into the sinus node artery of dogs.[25] In man sinoatrial block[26] and symptomatic bradycardia requiring pacing[6] have been described during treatment with amiodarone. In addition to the patients we have described, sinus arrest has been reported during treatment with amiodarone in both the presence and absence of concomitant administration of digoxin.[27 28] On the other hand, amiodarone has been used with apparent benefit in a small number of patients with the tachycardia-bradycardia syndrome.[29] We do not know whether amiodarone alone, or the combination of cardioactive drugs used, accounted for these responses in our patients.

Most antiarrhythmic agents currently in use are capable of exacerbating ventricular arrhythmias.[30] The incidence appears to be a function of the individual drug and the patient population in which it is used. Worsening of arrhythmias may occur with serum concentrations within the "therapeutic" range and without other evidence of toxicity. We attribute the development of incessant ventricular tachycardia in four of our patients to the action of amiodarone for several reasons. Firstly, there was clear

evidence of an effect of amiodarone on electrophysiological variables—for example, prolonged refractory periods— although the patients had been taking the drug for a relatively short period. Secondly, the incessant ventricular tachycardia was unresponsive to parenteral drug treatment that had previously been successful; and, thirdly, ventricular tachycardia subsided in three of these patients after a period of time directly related to the duration of treatment with amiodarone. In one patient the haemodynamic instability of the incessant arrhythmia was such as to require emergency map guided aneurysmectomy. No patient had acute myocardial ischaemia, electrolyte abnormalities, or increased cardiac failure that might have provoked these arrhythmias.

Digitalis toxicity alone is unlikely to have accounted for these severe arrhythmias given the serum digoxin concentrations measured at the time of their onset in the three patients taking digoxin.[31] Prolongation of the QTc interval, as measured by Bazett's method, although present in each case, was not helpful in distinguishing the patients who developed incessant arrhythmias. Amiodarone invariably prolonged the QTc interval in our patients, and it is not clear whether excessive prolongation of this variable predisposes patients to spontaneous arrhythmias. Two cases of ventricular fibrillation and polymorphic ventricular tachycardia during treatment with amiodarone and associated with prolonged QT intervals have been reported.[32 33] In our cases recurrent ventricular tachycardia was uniform in morphology and identical with that observed before the introduction of amiodarone but substantially slower in rate, which is also consistent with an effect of amiodarone. Interestingly, the successful treatment of syncope with amiodarone in two cases of the syndrome of idiopathic long QT intervals has been reported.[34] Recently, a case report of aggravation of ventricular tachycardia by amiodarone has been published.[12]

The high incidence of neurological and gastrointestinal side effects is similar to that in other reports.[6 16] Increased liver enzyme activity and fatty infiltration of the liver in association with amiodarone has been previously described.[35] Thyroid, dermatological, and ophthalmological changes have been discussed in detail by others,[1] and our findings confirm these earlier reports.[17 18]

Amiodarone in the presence of warfarin lowers the level of vitamin K dependent coagulation factors by an unknown mechanism.[36 37] This may be reversed by giving vitamin K. Moysey *et al* reported digitalis toxicity in several of their patients when amiodarone was added to their regimens and called attention to the possible confusion of digitalis toxicity with adverse reactions from amiodarone.[38] Combinations of cardioactive drugs may be important in the pathogenesis of some of the reactions we report, and hence the indication for treatment with digoxin in individual patients must be carefully examined. Because many of the patients in whom amiodarone is useful require multiple drug regimens potential complications of such treatment must be anticipated. Maintenance doses of digoxin and warfarin should be reduced when amiodarone is added.

Conclusions—Amiodarone is effective in many patients whose arrhythmias are refractory to other drugs. Use of amiodarone, however, is associated with a high incidence of adverse reactions, and although some of these are dose related and many are tolerable, a disturbing number of serious and potentially life threatening responses occur. Further study to define methods of avoiding or limiting adverse reactions with amiodarone, or finding safer yet effective alternative treatments, must be pursued. We believe that these observations emphasise the need to restrict the use of amiodarone at present to patients who are unresponsive to, or intolerant of, other antiarrhythmic drugs. Furthermore, continued close observation of all patients being treated with this agent is necessary.

We thank Drs C Hales and L Fang for helpful discussion of some of these cases. Dr S Rosenthal provided statistical advice. We also thank Ellen DiBiase for secretarial help.

This work was supported in part by National Institutes of Health grant RO1 HL 25992. JNR is the recipient of an American Heart Association established investigatorship (E181-177).

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(*Accepted 12 April 1983*)

SHORT REPORTS

Bilateral ulnar and radial nerve palsies as a complication of childbirth

Iatrogenic bilateral ulnar nerve palsies have resulted from the use of walking frames[1] and operating tables.[2] With the former the injury is at the wrist and with the latter at the elbow. Theoretically, iatrogenic bilateral radial nerve palsies could occur in the axillae owing to incorrectly fitted crutches, but to our knowledge this has never been reported. We report a case of bilateral radial and ulnar nerve palsies in a patient as a result of childbirth using a birthing stool.

Case report

A 31 year old pregnant woman was admitted to the labour ward at 39 weeks' gestation having had uterine contractions for seven and a half hours. She had had one previous full term normal vaginal delivery with an uneventful labour and there was no relevant medical or family history. About two hours after admission she had a fully dilated cervix and a vertex presentation. She chose to use our three legged wooden birthing stool (supplied by Crewdys Wood Products) during the second stage with her husband sitting in a standard office chair behind her to provide support. Instead of passing his hands under her axillae so as to support her with his forearms, he placed his hands in her axillae. Throughout the second stage, which lasted 20 minutes, she noticed numbness and tingling in both her hands but ignored it so as to concentrate on pushing. After a normal vaginal delivery of a normal birthweight baby girl the numbness and paraesthesia persisted and was accompanied by weakness of both arms. On examination she was found to have sensory and motor deficits attributable to bilateral radial and ulnar nerve palsies; the details are shown in the table. She also complained of slight tenderness in the lateral wall of both axillae. Over the next five days there was a slight improvement in the power of all her muscles, and the sensory symptoms and signs in the radial nerve distribution resolved bilaterally. Three weeks later her condition was virtually unchanged.

Details of sensory and motor deficits of arm muscles due to bilateral radial and ulnar nerve palsies

	Left arm	Right arm
Sensory deficit		
Dorsum of first web space	Tingling	Tingling
Ulnar border of hand and little finger	Numbness	Numbness
Motor deficit		
Biceps	5	5
Triceps	1	1
Flexor carpi radialis	5	5
Flexor digitorum superficialis	5	5
Flexor carpi ulnaris	2	1
Flexor digitorum profundus:		
Index and middle finger	5	5
Ring and little finger	2	1
Flexor palmaris longus	5	5
Extensor carpi radialis	1	1
Extensor digitorum communis	1	1
Extensor carpi ulnaris	1	1
Brachioradialis	1	1
Thenar eminence	5	5
Other intrinsic hand muscles	2	1

Muscle power grading: 0 = total paralysis, 1 = barely detectable contracture, 2 = not enough power to act against gravity, 3 = strong enough to act against gravity, 4 = still stronger but less than normal, 5 = full power.

Comment

To our knowledge this is the first reported case of both bilateral radial and ulnar nerve palsies and a maternal nerve palsy as a complication of childbirth. Teres major and latissimus dorsi form the posterior axillary wall over which the arm's neurovascular bundle passes directly anteriorly. Within this neurovascular bundle the radial nerve lies posteriorly, and the ulnar nerve is the most medially placed structure and lies posteriorly to the axillary vessels and median nerve. Apparently, her husband's finger tips compressed the radial and ulnar nerves against the posterior axillary wall and pushed the other, more anteriorly placed, neurovascular structures superiorly into the axilla. Fortunately, her husband did not compress the neurovascular bundle against the posterior axillary wall 2 cm more proximally, as he may then have also damaged the axillary nerve causing weakness of shoulder abduction.

Since bilateral ulnar and radial nerve palsies can occur with this method of delivery, delivery suite staff need to be aware of this danger.

We thank Mr D McCoy, consultant obstetrician, for allowing us to report this case.

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(*Accepted 15 April 1983*)

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Oxidative haemolysis after administration of doxorubicin

Deficiency of glucose-6-phosphate dehydrogenase (G6PD) is the most common enzyme deficiency in red blood cells and has been found in 11·2% of black men in hospital.[1] Infections and certain drugs may induce haemolysis in patients with this defect. We describe a patient with G6PD deficiency who developed acute haemolytic anaemia after treatment with doxorubicin.

Case report

A 58 year old black man was admitted to hospital for investigation of an enlarging thigh mass and increasing shortness of breath. Seven years previously G6PD A⁻ deficiency had been diagnosed, although he denied any knowledge of haemolytic episodes. On examination he had a firm mass measuring 16×20 cm on the right thigh. An enlarged right inguinal node was also present. Laboratory results showed a haemoglobin concentration of 14·8 g/dl (1·2% reticulocytes); chest *x* ray examination showed multiple