Plasma amiodarone concentrations during intravenous infusion

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Amiodarone is a useful antiarrhythmic agent whose pharmacokinetics are incompletely characterised. In order to optimise efficacy of an antiarrhythmic drug, information regarding plasma concentrations achieved during use of the drug is necessary. We report plasma amiodarone and desethylamiodarone concentrations in eight patients following intravenous infusion at a rate of 175 mg h⁻¹ for the first 2 h, followed by infusion at a rate of 50 mg h⁻¹ for a further 46 h a regimen very similar to that recommended by the manufacturers. In at least three of eight patients plasma concentrations were below the suggested therapeutic range of 1.0–2.5 mg l⁻¹ from 3 to 16 h after the infusion was started. Our data suggests that larger doses of intravenous amiodarone than those previously recommended may be necessary to obtain optimal benefit from the drug.

Keywords amiodarone infusion

Introduction

Amiodarone hydrochloride, a benzofuran derivative, has been demonstrated to be an effective antiarrhythmic agent for the treatment of supraventricular and ventricular arrhythmias (Graboyes *et al.*, 1983; Heger *et al.*, 1983). Amiodarone has an unusual pharmacokinetic profile which is, as yet, incompletely characterised (Latini *et al.*, 1984), in particular the terminal elimination half-life may be as long as 100 days.

Treatment of possibly life-threatening arrhythmias requires the rapid achievement and maintenance of therapeutic concentrations of a drug. To achieve this high-dose oral amiodarone therapy may be given initially but such oral therapy can be limited by gastrointestinal side effects most commonly nausea or constipation (Greene *et al.*, 1983; McGovern *et al.*, 1983). An alternative approach is intravenous infusion of amiodarone, but information regarding drug concentrations achieved during therapeutic use of amiodarone infusion is sparse. We therefore examined the plasma concentrations of amio-

darone and its desethyl metabolite achieved in eight patients during infusion of amiodarone.

Methods

Eight patients (five male), aged 46–74 years and weighing 45–91 kg (68.9 ± 16.8 kg (mean ± s.d.)) were treated with an amiodarone infusion. Four patients had ischaemic heart disease, two had aortic valve disease (one also had ischaemic heart disease), one had hypertrophic cardiomyopathy, and one an atrial septal defect. One patient had an apparently normal heart apart from her arrhythmia. One patient had recurrent ventricular tachycardia and five patients had refractory paroxysmal supraventricular tachyarrhythmias (one following coronary artery surgery). In two patients amiodarone was used as prophylaxis against recurrence of atrial fibrillation following cardioversion. Drugs used previously in these patients included lignocaine,

β -adrenoceptor blockers, digoxin, verapamil, phenytoin and disopyramide. All other antiarrhythmic therapy was discontinued during the amiodarone infusion. Urea was elevated to 13.2 mmol l^{-1} in one patient and aspartate aminotransferase to 85 iu l^{-1} and 102 iu l^{-1} (normal range $5\text{--}35 \text{ iu l}^{-1}$) in two patients. No patient was in cardiac failure.

Using data of Riva *et al.* (1982) and the modelling method of Shand *et al.* (1981) we chose an infusion regimen of 175 mg h^{-1} for 2 h followed by 50 mg h^{-1} for 46 h. Amiodarone was administered in 5% dextrose via a long intravenous catheter from an antecubital vein or via a central venous catheter. This regimen differs little from the manufacturer's recommendations of 5 mg kg^{-1} over 2 h followed by 50 mg h^{-1} for 46 h. After the infusion patients were transferred to oral amiodarone therapy, initially at a dose of 200 mg three times daily. The study was approved by the hospital ethics committee. Informed written consent was obtained from each patient for repeated blood sampling.

The relationship between patient weight and peak plasma amiodarone concentrations was examined using the method of least squares. Statistical significance was assumed if $P < 0.05$.

Results

Plasma amiodarone concentrations (Figure 1) rose rapidly after the infusion was started and at

30 min the mean concentration was 1.42 ± 0.83 (s.d.) mg l^{-1} . The mean peak amiodarone level was $1.92 \pm 0.48 \text{ mg l}^{-1}$ 2 h after the infusion was started. Plasma concentrations then fell to a minimum of $0.97 \pm 0.38 \text{ mg l}^{-1}$ at 5 h. Thereafter mean plasma concentrations rose gradually, and at 48 h were $1.57 \pm 0.32 \text{ mg l}^{-1}$.

Between 3 and 16 h the plasma amiodarone concentrations were below 1.0 mg l^{-1} in at least three of the eight patients studied.

Desethylamiodarone (DA) concentrations were significantly lower than amiodarone concentrations throughout the infusion. Desethylamiodarone concentrations tended to rise slowly during the latter part of the infusion but at 48 h were only $0.18 \pm 0.06 \text{ mg l}^{-1}$.

Adverse effects occurred in two patients. Severe sinus bradycardia occurred in one patient after 12 h amiodarone infusion, when the plasma amiodarone concentration was 1.47 mg l^{-1} . She had recently been taking disopyramide. One patient had mild thrombophlebitis at the distal end of a long intravenous cannula inserted from an antecubital vein.

In one patient paroxysmal atrial fibrillation occurred after 7 h infusion (the plasma amiodarone concentration at 6 h was 0.69 mg l^{-1}).

We did not find a significant relationship between body weight and peak plasma amiodarone concentration ($r = 0.575$, $n = 8$, $P > 0.05$) or trough concentration ($r = 0.562$, $n = 8$, $P > 0.05$).

Figure 1 Mean plasma amiodarone concentrations (mg l^{-1}) (●) and range (○) during amiodarone infusion. Provisional therapeutic range of $1.0\text{--}2.5 \text{ mg l}^{-1}$ is indicated by hatched lines.

Discussion

Knowledge of the relationship between the antiarrhythmic effectiveness of amiodarone and its plasma concentrations is still limited. This uncertainty is increased because of differences in electrophysiological effects of oral and intravenous amiodarone (Wellens *et al.*, 1984). Therefore a suggested therapeutic range of 1.0–2.5 mg l⁻¹ (Latini *et al.*, 1984) must be regarded as provisional. Haffajee *et al.* (1983) described relapse of arrhythmias when plasma concentrations fell below 1.0 mg l⁻¹ during chronic oral therapy, and a tendency to increased adverse effects above a plasma concentration of 2.5 mg l⁻¹. Staubli *et al.* (1983) commented on good arrhythmia control above a concentration of approximately 1 mg l⁻¹ and increased side effects above a concentration of approximately 2.5 mg l⁻¹. During chronic oral therapy cardiac tissue concentrations of amiodarone appear to exceed those in plasma (Adams *et al.*, 1983). If such increased cardiac amiodarone concentrations are important in the antiarrhythmic effects of amiodarone or if amiodarone concentrations at myocardial receptors are lower than plasma concentrations during intravenous loading then the therapeutic range of plasma amiodarone concentrations during intravenous administration may be higher than the range of 1.0–2.5 mg l⁻¹ during chronic oral therapy. The electrophysiological actions of desethylamiodarone have yet to be defined, but if this metabolite contributes significantly to the antiarrhythmic effects of oral amiodarone during chronic therapy, the therapeutic range for intravenous amiodarone may have to be revised upwards. Thus it may be seen that using the therapeutic range for chronic oral therapy would tend to underestimate any deficiencies of the infusion regimen which we describe. Despite this, mean plasma amiodarone concentrations were below the suggested therapeutic range at 5 and 6 h. At all sample times between 3 h and 16 h

of infusion, plasma concentrations below 1.0 mg l⁻¹ were observed in at least three of the eight patients. To minimise the pronounced fall in plasma concentrations a three step infusion may be needed. The modelling technique of Shand *et al.* (1981) predicts a trough level of 1.3 mg l⁻¹ at 3 h and a further trough of 1.3 mg l⁻¹ at 18 h using an infusion of amiodarone at a rate of 175 mg h⁻¹ for 2 h followed by infusion of 100 mg h⁻¹ for 10 h and 50 mg h⁻¹ for a further 36 h. A three step infusion regimen is less convenient than a two step one, but may be more appropriate than the manufacturer's current recommendations in situations where arrhythmia recurrence could be life threatening.

Our infusion regimen differs little from that recommended by the manufacturers, but appears to produce suboptimal plasma concentrations. The recurrence of arrhythmia (as occurred in one of our patients) during the period of suboptimal plasma concentrations could be erroneously interpreted as a failure of antiarrhythmic efficacy of amiodarone. We suggest that any studies examining efficacy or otherwise of the infusion regimen used in this study, should take account of the data presented here.

Our data show considerable interindividual variability in drug concentrations achieved, which has also been described during oral therapy (Riva *et al.*, 1982). The mechanism for this interindividual variability following intravenous administration of amiodarone is unclear. Differences in the volume of distribution of the drug could be responsible for the variability in early plasma concentrations. Our data do not suggest that body weight is related to observed interindividual differences.

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References

- Adams, P. C., Nicholson, M. R., Storey, G. C. A., Holt, D. W. & Campbell, R. W. F. (1983). Amiodarone tissue distribution: relation to adverse effects (Abstract). *Br. Heart J.*, **49**, 297.
- Graboyes, T. B., Podrid, P. J. & Lown, B. (1983). Efficacy of amiodarone for refractory supraventricular tachyarrhythmias. *Am. Heart J.*, **106**, 870–876.
- Greene, H. L., Graham, E. L., Werner, J. A., Sears, G. K., Gross, B. W., Gorham, J. P., Kudenchuk, P. J. & Trobaugh, G. B. (1983). Toxic and therapeutic effects of amiodarone in the treatment of cardiac arrhythmias. *J. Am. Coll. Cardiol.*, **2**, 1114–1128.
- Haffajee, C. I., Love, J. C., Canada, A. T., Lesko, L. J., Asdourian, G. & Alpert, J. S. (1983). Clinical pharmacokinetics and efficacy of amiodarone for refractory tachyarrhythmias. *Circulation*, **67**, 1347–1355.
- Heger, J. J., Prystowsky, E. N. & Zipes, D. P. (1983).

- Clinical efficacy of amiodarone in treatment of recurrent ventricular tachycardia and ventricular fibrillation. *Am. Heart J.*, **106**, 887-894.
- Hutchings, A., Watt, A. H., Spragg, B. P., Stephens, M. R. & Routledge, P. A. (1985). A high performance liquid chromatographic assay of amiodarone and desethylamiodarone in plasma. *Br. J. clin. Pharmac.*, **20**, 299P.
- Latini, R., Tognoni, G. & Kates, R. E. (1984). Clinical pharmacokinetics of amiodarone. *Clin. Pharmacokin.*, **9**, 136-156.
- McGovern, B., Garan, H., Kelly, E. & Ruskin, J. N. (1983). Adverse reactions during treatment with amiodarone hydrochloride. *Br. med. J.*, **287**, 175-180.
- Riva, E., Gerna, M., Latini, R., Giani, P., Volpi, A. & Maggioni, A. (1982). Pharmacokinetics of amiodarone in man. *J. cardiovasc. Pharmac.*, **4**, 264-269.
- Shand, D. G., Desjardins, R. E., Bjornsson, T. D., Hammill, S. C. & Pritchett, E. L. C. (1981). The method of separate exponentials: a simple aid to devising intravenous drug-loading regimens. *Clin. Pharmac. Ther.*, **29**, 542-547.
- Staubli, M., Bircher, J., Galeazzi, R. L., Remund, H. & Studer, H. (1983). Serum concentrations of amiodarone during long-term therapy. Relation to dose, efficacy and toxicity. *Eur. J. clin. Pharmac.*, **24**, 485-494.
- Wellens, H. J. J., Brugada, P., Abdollah, H. & Dassen, W. R. (1984). A comparison of the electrophysiologic effects of intravenous and oral amiodarone in the same patient. *Circulation*, **69**, 120-124.

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