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Original Article

Systematic review of the use of intravenous amiodarone and nifekalant for cardiopulmonary resuscitation in Japan ☆

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ABSTRACT

Background: Intravenous amiodarone is considered to be the first-line drug for the treatment of ventricular tachycardia or fibrillation. However, in Japan, nifekalant had been used before the introduction of amiodarone; therefore, most clinical studies on amiodarone use have been small-scale studies. The aim of the present study was to review the literature concerning the actual use of amiodarone and nifekalant in order to evaluate the effects of both drugs and the most appropriate mode of administration.
Methods: The Japan Medical Abstracts Society, PubMed, and Scopus databases were used to identify the reports. The resulting data were used for a systematic review focusing on the effectiveness of amiodarone in comparison with that of nifekalant and the dose differential effect of amiodarone.
Results: The search returned 9 studies, including 310 patients, that compared the effectiveness of amiodarone and nifekalant, as well as 3 studies, including 108 patients, that analyzed the effectiveness of treatment according to amiodarone dose. Of 418 patients, 187 in whom amiodarone was used for cardiopulmonary resuscitation (CPR) were included in a review that compared the doses recommended by Japanese guidelines 2009 (125 mg intravenous [i.v.] over 10 min) and the American Heart Association guidelines (300 mg bolus i.v.). Amiodarone and nifekalant were equally effective in preventing electrical storm (67% vs. 67%). The defibrillation effect for CPR was also equal in the 2 groups (60% vs. 54%). Hypotension and bradycardia were recorded as adverse effects in the amiodarone group (9.5% and 5.3%), whereas torsades de pointes was observed in the nifekalant group (1.4%). In the analysis of the dose-differential effect of amiodarone, the rates of successful return of spontaneous circulation and discharge survival were higher in the 125-mg slow i.v. group than in the 300-mg bolus i.v. group (76% vs. 53% and 54% vs. 26%, respectively).
Conclusions: Amiodarone and nifekalant were equivalent in their prophylactic and defibrillation efficacy. Concerning the initial amiodarone dose, the 125 mg intravenous [i.v.] over 10 min seemed to be more appropriate for the Japanese population.

1. Introduction

Intravenous amiodarone has been established as the first-line drug for cardiopulmonary resuscitation (CPR) in patients with fatal ventricular arrhythmias [1]. However, in Japan, intravenous (i.v.) nifekalant hydrochloride was in common use from 1999 until i.v. amiodarone was approved in June 2007. Nifekalant interferes with the delayed rectifier K^+ channels, particularly the rapid component of the I_{Kr} current, as well as the inward rectifier I_{K1} current and the transient outward I_{to} channel [2,3]. In contrast, amiodarone has multiple effects, including blockade of the beta-adrenergic receptors, the fast inward Na^+ current, the L-type Ca^{2+} current, and the fast and slow components of the delayed rectifier K^+ current (I_{Kr} and I_{Ks}) [4]. According to the 2005 CPR guidelines of the American Heart Association (AHA) [1], 300 mg of i.v. amiodarone should be used for the initial dose. The following recommendations have been issued in Japan as a first guideline [5]: (1) 125 mg/10 min i.v. for the initial dose, (2) 50 mg/h drip i.v. (d.i.v.) for 6 h, and (3) 25 mg/h d.i.v. for maintenance.

We have used nifekalant for CPR and for the first time reported the favorable defibrillation effect of nifekalant in the treatment of refractory ventricular tachycardia and fibrillation (VT/VF) [6–8]. We also compared the usefulness of amiodarone with that of nifekalant and reported that the defibrillation efficacy was

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equivalent between these drugs [9]. In contrast, Yoshioka et al. [10] reported the dynamic variance of the ventricular late potentials induced by the Na^+ channel-blocking action of intravenous amiodarone and suggested the possibility of a negative chronotropic action of amiodarone when delivered i.v. for CPR.

Amiodarone has been used in Japan for more than 5 years now since its approval in July 2007, and intravenous amiodarone has been widely used for life-threatening ventricular tachycardia in the setting of critical care medicine. However, only few reports have been published in the international literature about the effects of amiodarone in a Japanese population. The purpose of this paper was to review the literature concerning the K^+ channel blockers amiodarone and nifekalant and to discuss the effects of both drugs and the most appropriate mode of administration.

2. Material and methods

2.1. Literature search

The Japan Medical Abstracts Society, PubMed, and Scopus databases were used to identify abstracts, national proceedings, and Japanese or English papers for systematic review, using the following keywords: "nifekalant," "amiodarone," "VT/VF," "cardiopulmonary arrest (CPA)," and "CPR." Articles published between July 2007 and December 2012 were retrieved. Case reports from single centers were excluded. All the subjects were Japanese.

Two public reliable meta-analysis software, Review Manager (Rev Man) [11] and GRADE profiler [12], were used in the statistical analysis. A forest plot was constructed to investigate any inconsistency of results. A funnel plot was used for evaluating whether a publication bias exists. A general variance-based method was used for the calculation of odds ratio (OR) and confidence interval (CI) in a meta-analysis. However, a simple pooled analysis was used in the case of an inappropriate meta-analysis. Significant differences were computed using the chi-square ($n \geq 5$) and Fisher exact tests ($n < 5$).

3. Results

3.1. Studies comparing outcomes between nifekalant and amiodarone

- The search results included 9 articles [13–20] that compared "the effects of amiodarone and nifekalant (defined study 1)" and 3 articles [21–23] comparing "the effects of different doses of amiodarone (defined study 2)."
- Eight articles [13–15,19,21–23] were from the conference proceedings of the Amiodarone Workshop (Japanese). Two articles [17,18] were original papers in Japanese, one [9] an original paper in English and the other [20] a conference abstract from the *Journal of Arrhythmia*.
- Eleven articles [13–23] were retrospective observational studies, and the other one [9] was a prospective study.

All these articles were published between 2010 and 2012. Study 1 included 310 patients (Table 1), of whom 196 were in-hospital cases and 114 were out-of-hospital cases. The main issues focused on by the studies were as follows:

- Prevention of recurrent ventricular arrhythmias, by Sasaki et al. [13] ($n=42$)
- Prophylactic effect on electrical storm (ES), by Sasaki et al. [13] ($n=12$), Maeda et al. [14] ($n=7$), Miyauchi [15] ($n=21$), and Mera et al. [16] ($n=74$).
- Defibrillation effect on VT/VF for in-hospital CPA patients, by Takahashi et al. [17] ($n=40$).
- Defibrillation effect on VT/VF for out-of-hospital CPA patients, by Amino et al. [9] ($n=30$), Ito et al. [18] ($n=39$), Hayakawa et al. [19] ($n=24$), and Yamamoto et al. [20] ($n=21$).

Generally, ES was defined as a serious and intractable arrhythmia attack in which VT/VF appears more than 2 or 3 times within 24 h, requiring direct current shock. *Prevention* was defined as the breakdown of ES and inhibition of VT/VF recurrences.

The rate of preventative effect against ventricular arrhythmias was 74% for amiodarone and nifekalant by 1 institution report ($p=0.74$) [13]. The prophylactic effects of amiodarone and nifekalant against ES were similar ($p=0.99$) in 4 institution reports [13–16]. The defibrillation effect on VT/VF in the patients undergoing in-hospital CPA had no significance between the amiodarone and nifekalant groups (73% vs. 48%, $p=0.29$) by 1 institution report [17]. The success rates of defibrillation by amiodarone and nifekalant in the patients undergoing out-of-hospital CPA were similar ($p=0.93$) in 4 institution reports [9,18–20]. Meta-analysis was applied to the studies on "the prophylactic effect of ES" and "defibrillation of VT/VF for out-of-hospital CPA." The results (Fig. 1) showed no significance between amiodarone and nifekalant in terms of prophylactic effect (OR, 1.02; 95% CI, 0.45–2.29; Fig. 1A) and in the investigation of defibrillation success (OR, 1.39; 95% CI, 0.60–3.06; Fig. 1B). These class III antiarrhythmic drugs clearly demonstrated more than 50% efficacy for treating any fatal arrhythmia. However, publication bias was not evaluated by the statistical analysis of the funnel plot because of the small number of publications included.

The frequency rates of adverse effects in the patients in whom defibrillation with amiodarone was successful ($n=75$) were as follows: hypotension, 12.0%; bradycardia, 9.3%; and severe QT prolongation (>600 ms), 5.3%. In the nifekalant group ($n=71$), no hypotension or bradycardia occurred, but severe QT prolongation was observed in 12.7% of the patients and torsades de pointes was observed in 1.4%.

3.2. Patient population in study 1

Of the total 310 patients, 152 were designated as the amiodarone group and 158 were designated as the nifekalant group. The demographic and clinical data of the patients in study 1 are shown in Table 2. The patient age was specified for 163 patients; the mean $\pm$ SD age was 64 ± 15.3 years ($n=86$) in the amiodarone group and 64 ± 16.8 years ($n=77$) in the nifekalant group. Sex was specified for 103 of the 310 patients; the ratio of the male subjects was 75% (40/53) in the amiodarone group and 76% (38/50) in the nifekalant group. The targeted fatal arrhythmia was 25VT, 25VF, and 3VT/VF in the amiodarone group ($n=53$) and 23VT, 23VF, and 3VT/VF in the nifekalant group ($n=49$). The time interval from basic life support to anti-arrhythmic drug administration was 54 ± 29.8 min ($n=57$) in the amiodarone group and 47 ± 17.9 min in the nifekalant group ($n=36$). For the 93 patients who underwent laboratory examinations, the arterial blood pH on arrival was 7.04 ± 0.21 ($n=57$) in the amiodarone group and 7.04 ± 0.19 ($n=36$) in the nifekalant group. For the 54 patients, the serum K^+ level on arrival was 4.9 ± 0.8 mEq/L ($n=32$) in the amiodarone group and 4.6 ± 0.9 ($n=22$) in the nifekalant group. The underlying disease was specified for 84 patients as follows. Of the 36 patients in the amiodarone group, ischemic heart disease was observed in 16 (44%); cardiomyopathy, in 12 (33%); and other conditions, in 8 (22%). Of the 48 patients in the nifekalant group, ischemic heart disease was observed in 20 (47%); cardiomyopathy, in 14 (33%); and other conditions, in 9 (19%). For the 72 patients who underwent an echocardiographic examination, the ejection fraction (EF) was $42\% \pm 2.8\%$ in the

Table 1
Comparison between the effectiveness of amiodarone and that of nifekalant.

No.	Author	Content of study	$n=310$ (Male)	Amiodarone (n) / Nifekalant (n)	Mean age (years)	Effective examples, n (%)	p	Complications
1	Sasaki et al. [13]	Prevention of the recurrent ventricular arrhythmias	42 (28)	19	69	14 (74)	0.74	4 hypotension 2 bradycardia 4 prolonged excessive QT
				23	66	17 (74)		2 prolonged excessive QT 1 TdP
		Prophylactic effect of electrical storm	12 (–)	3	–	1 (33)		
				9	–	6 (67)		
2	Maeda et al. [14]	Prophylactic effect of electrical storm	7 (4)	2	62	1 (50)		
				5	69	3 (60)		
3	Miyauchi et al. [15]	Prophylactic effect of electrical storm	21 (–)	8	65	5 (63)	0.99	
				13	65	8 (62)		
4	Mera et al. [16]	Prophylactic effect of electrical storm	74 (–)	41	–	29 (71)		4 hypotension 4 bradycardia
				33	–	23 (70)		3 prolonged excessive QT
5	Takahashi et al. [17]	Defibrillation of VT/VF for in-hospital CPA	40 (–)	11	–	8 (73)	0.29	
				29	–	14 (48)		
6	Amino et al. [9]	Defibrillation of VT/VF for out-of-hospital CPA	30 (24)	15	65 ± 14.4	10 (67)		1 hypotension 1 bradycardia
				15	62 ± 16.3	7 (47)		0
7	Ito et al. [18]	Defibrillation of VT/VF for out-of-hospital CPA	21 (–)	11	–	6 (55)		
				10	–	5 (50)	0.93	
8	Hayakawa et al. [19]	Defibrillation of VT/VF for out-of-hospital CPA	24 (22)	17	61 ± 15.6	7 (41)		
				7	59 ± 19.0	2 (29)		
9	Yamamoto et al. [20]	Defibrillation of VT/VF for out-of-hospital CPA	39 (–)	25	65 ± 16	18 (72)		
				14	64 ± 15	11 (79)		

VT/VF: ventricular tachycardia/fibrillation, CPA: cardiopulmonary arrest, TdP: torsade de pointes.

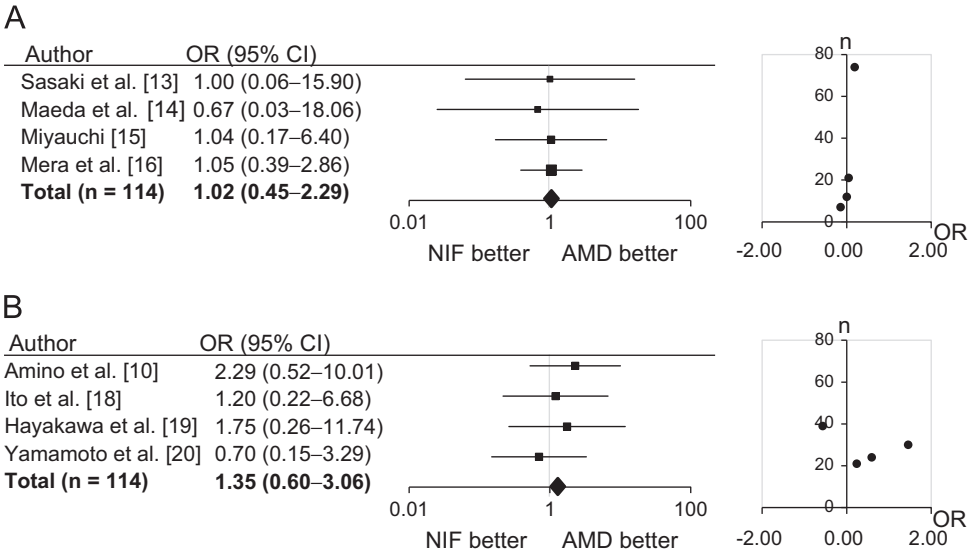

Fig. 1. Results of the meta-analysis. (A) Forest and funnel plots of the prophylactic effect of electrical storm. (B) Forest and funnel plots of successful defibrillation effect for out-of-hospital VT/VF. No significant comparative merits were found between amiodarone and nifekalant. OR: odds ratio, CI: confidence interval, NIF: nifekalant, AMD: amiodarone.

amiodarone group ($n=34$) and $36\% \pm 2.8\%$ in the nifekalant group ($n=38$).

3.3. *Differential effect of amiodarone dose (study 2)*

Three single-center reports were related to evaluations of different doses of amiodarone (Table 3). These were retrospective studies including 108 CPA patients. Kobori et al. [21] evaluated the return of spontaneous circulation (ROSC) rate in patients with in-hospital/out-of-hospital CPA, comparing the following 2 different regimens: (i) 125 mg slow i.v. ($n=28$) and (ii) 150–300 mg i.v. ($n=26$). "Slow i.v." means a bolus injection over 10 min, according to the guidelines of the Japanese Circulation Society [5]. The ROSC rate was 93% in the former group and 46% in the latter. However, no clear conclusions could be drawn because of the uneven distribution of the population backgrounds (age, underlying disease, cardiac function, etc.). Matsuo et al. [22] investigated the hospitalization rate and discharge survival rate in the patients with out-of-hospital CPA in the following 2 groups: (i) 300 mg i.v. ($n=15$) and (ii) 300 mg + additional 150 mg i.v. ($n=19$). The ROSC success rate was

Table 2
Patient populations in the studies comparing outcomes between nifekalant and amiodarone.

	Specified number of patients (n/310)		Amiodarone	Nifekalant
Age, years	163		64 ± 15.3	64 ± 16.8
Sex (male)	103		40 (75%)	38 (76%)
Targeted fatal arrhythmia	102	VT	25 (47%)	23 (46%)
		VF	25 (47%)	23 (46%)
		VT/VF	3 (6%)	3 (6%)
Time interval from basic life support to anti-arrhythmic drug administration	93		54 ± 29.8 min	47 ± 17.9 min
Atrial blood pH on arrival	93		7.04 ± 0.21	7.04 ± 0.19
Serum K^+ level (mEq/L) on arrival	54		4.9 ± 0.8	4.6 ± 0.9
Underlying disease	84	Ischemic heart disease	16 (44%)	20 (47%)
		Cardiomyopathy	12 (33%)	14 (33%)
		Others	8 (22%)	9 (19%)
EF (%) examined by echocardiography	72		42 ± 2.8%	36 ± 2.9%

EF: ejection fraction, VT/VF: ventricular tachycardia/fibrillation.

Table 3
Dose differential effect of amiodarone.

No.	First author	Content of study	n=108 (Male)	Mean age, years		ROSC success (%)	Complications
1	Kobori et al. [21]	Defibrillation effect of VT/VF by amiodarone for in-hospital CPA/out-of-hospital CPA	54 (46)	63 ± 14	125 mg slow i.v.	26/28 (93%)	1 bradycardia 1 hypotension
					150–300 mg i.v. (mean, 283 mg)	12/26 (46%)	8 PEA/ asystole
2	Matsuo et al. [22]	Defibrillation effect of VT/VF by amiodarone for out-of-hospital CPA	34 (26)	58	300 mg i.v.	12/15 (80%)	
					300 mg i.v.+additional 150 mg i.v.	9/19 (47%)	
3	Kubo et al. [23]	Defibrillation effect of VT/VF by amiodarone for out-of-hospital CPA	20 (32)	41	125 mg slow i.v.	3/3 (100%)	
					300 mg i.v.	5/9 (56%)	
					300 mg i.v.+additional 150 mg i.v.	5/8 (63%)	

VT/VF: ventricular tachycardia/fibrillation, CPA: cardiopulmonary arrest, ROSC: return of spontaneous circulation, PEA: pulseless electrical activity.

80% in the former group and 47% in the latter. However, according to the authors, no significant difference was found between the groups (reason unknown). Kubo et al. [23] studied the ROSC and discharge survival rates in the patients with out-of-hospital CPA, comparing the following 3 groups: (i) 125 mg slow i.v. (n=3), (ii) 300 mg i.v. (n=9), and (iii) 300 mg+additional 150 mg i.v. (n=8). The ROSC success rate was 100%, 56%, and 47%. However, no significant differences could be determined between the 3 groups, possibly because of the small number of subjects in the first group. Although these 3 reports did not provide significant statistical findings regarding the effectiveness of different doses of i.v. amiodarone, the results appear to suggest that slow injection with a minimal dose might have an advantage in terms of CPR outcomes.

Regarding the adverse effects of amiodarone, Kobori et al. [21] reported that the 125-mg slow i.v. group showed comparatively less-severe events (1 case of bradycardia and 1 of hypotension), whereas the 150- to 300-mg i.v. group exhibited severe events, leading to pulseless electrical activity (PEA) and asystole in 8 patients. Even after successful ROSC was achieved, the combined use of a catecholamine with amiodarone was needed in all 12 cases in the 150- to 300-mg i.v. group. These observations suggest that with higher doses of amiodarone, it becomes more difficult to maintain hemodynamic stability.

3.4. Japanese and AHA guidelines for amiodarone in CPR

As stated earlier, of the 418 (310+108) patients included in study 2, 187 were treated with amiodarone (Table 4). The subjects were all CPA cases. They were divided into 2 groups as follows: (i) lower dose (125 mg) with slow i.v., according to the Japanese guidelines 2009, and (ii) higher dose (almost 300 mg or more) as a bolus, based on the AHA guidelines. The Japanese guideline group consisted of 93 patients in 6 hospitals, and the AHA guideline group consisted of 94 patients in 4 hospitals. The ROSC success rate was 76% (71/93) in the former group and 53% (50/94) in the latter group. The discharge survival rate was reported for 82 of the 93 patients in the Japanese guideline group and for all 94 patients in the AHA guideline group. The rates were 54% (44/82) in the former group and 26% (24/94) in the latter group. Thus, a smaller dose with slow administration appeared to be better in terms of ROSC outcome and discharge survival. However, statistical analysis was not performed in this study.

4. Discussion

In study 1, which compared the effectiveness of amiodarone and nifekalant in 310 patients, both agents appeared to be almost equal in terms of prophylactic effect against ES and defibrillation effect in CPR. Hypotension and bradycardia were observed as adverse effects in the amiodarone group, and torsades de pointes was the adverse effect observed in the nifekalant group. In study 2, which compared the effectiveness of amiodarone doses in 187 patients, the ROSC success and discharge survival rates were higher in the 125-mg slow i.v. group than in the 300-mg bolus group. One report [21] suggested that PEA and asystole were more likely to occur in the high-dose amiodarone group.

4.1. Comparison between the effectiveness of amiodarone and that of nifekalant

This systematic review revealed that amiodarone and nifekalant were excellent for the prophylaxis of ventricular tachyarrhythmia and defibrillation during CPR. However, the discharge

Table 4
Comparison between the doses recommended by the Japanese and AHA guidelines.

	Subject	Method of amiodarone administration	$n=187$	ROSC success, n (%)	Survival discharge, n (%)
Japanese CPR guidelines					
Takahashi et al. [17]	IHCPA	125 mg slow i.v.	11	8 (73)	–
Amino et al. [9]	OHCPA	125 mg slow i.v.	15	10 (67)	8 (53)
Ito et al. [18]	OHCPA	125 mg slow i.v.	11	6 (55)	4 (36)
Yamamoto et al. [20]	OHCPA	125 mg slow i.v.	25	18 (72)	11 (44)
Kobori et al. [21]	IHCPA/OHCPA	125 mg slow i.v.	28	26 (93)	20 (71)
Kubo et al. [23]	OHCPA	125 mg slow i.v.	3	3 (100)	1 (33)
Total			93	71 (76)	44/82 (54)
AHA CPR guidelines					
Hayakawa et al. [19]	OHCPA	(150)–300 mg i.v. (average 237 mg)	17	7 (41)	5 (29)
Kobori et al. [21]	IHCPA/OHCPA	(150)–300 mg i.v. (average 283 mg)	26	12 (46)	8 (31)
Matsuo et al. [22]	OHCPA	300 mg i.v.	15	12 (80)	6 (40)
		300 mg i.v.+150 mg additional i.v.	19	9 (47)	2 (11)
Kubo et al. [23]	OHCPA	300 mg i.v.	9	5 (56)	1 (11)
		300 mg i.v.+150 mg additional i.v.	8	5 (63)	2 (25)
Total			94	50 (53)	24 (26)

CPA: cardiopulmonary arrest, IHCPA: in-hospital CPA, OHCPA: out-of-hospital CPA, ROSC: return of spontaneous circulation, PEA: pulseless electrical activity.

survival rate could not be examined because of the lack of information regarding the prognosis in the 310 patients. In our single-center comparative study between amiodarone and nifekalant [9], the discharge survival rate did not differ significantly between the 2 groups (53% vs. 21%, $p=0.06$). Notably, all 4 survivors in the nifekalant group were able to resume normal daily life after hospital discharge, whereas this was possible for only 2 of the 11 survivors in the amiodarone group. The difference was probably partly attributable to the longer time between drug administration and defibrillation success in the amiodarone patients than in the receiving nifekalant. Although amiodarone is now the first-line drug used for CPR, nifekalant could be viewed as a useful alternative.

Apart from some case reports, we found no data concerning the combined use of amiodarone and nifekalant. We previously reported that the consecutive use of nifekalant after lidocaine sometimes induced an unexpected effect in CPA patient; that is, the combination of the 2 drugs often provoked sudden asystole [6,7]. Regarding the mechanism of this serious adverse effect, we hypothesized that progression of metabolic acidosis is associated with CPA leading to reduced effects of intrinsic catecholamine and retard the pharmacological dissociation of Na^+ channel blocker. The absence of any atrial or ventricular escape rhythm suggest that severe hypoperfusion and drug administration might cause a diffuse suppressive effect on conduction involving the sinus node, atrioventricular node, and Purkinje fibers. Interaction between lidocaine and nifekalant increased the suppressive effect on I_{Kr}, I_{Ks}, and I_{Na} within the sinus node. Similar considerations apply to the multichannel blocker, amiodarone. The effects of intravenous amiodarone on cardiac Na^+ channels are similar to lignocaine (lidocaine) in terms of their blocking and unblocking kinetics [24]. Lidocaine-like Na^+ channel blocking action may play a dual role in the development of antiarrhythmia or proarrhythmia. If amiodarone and nifekalant are to be used at the same time, each half dose should be given cautiously.

4.2. Effectiveness according to amiodarone dose

In 2007, Katoh et al. [25] first reported the effectiveness of intravenous amiodarone in Japanese patients based on open-label, uncontrolled, multicenter studies conducted in 39 medical facilities. Amiodarone was administered as an initial infusion of 125 mg over 10 min. The dose levels were based on data from a dose-determination study conducted in the United States, after taking into account the difference in body weight between Americans and Japanese [26–28]. The efficacy and safety of the drug in preventing acute relapse of VT/VF were well demonstrated for this dose and delivery method. No severe effects related to amiodarone were observed to be associated with the method of initial infusion of 125 mg over 10 min.

The best-known large clinical studies are the ARREST [29] (amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation) and ALIVE [30] (amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation) trials. ARREST, whose findings were published in 1999, was the first study to confirm the effect of amiodarone for out-of-hospital CPA patients. Amiodarone or placebo was administered for defibrillator-resistant VT/VF. Among 504 subjects, primary survival from VT/VF was 44% (108/246) in the amiodarone group, compared with the 34% (89/258) in the placebo group ($p=0.03$). Three years later, ALIVE, in which lidocaine was used as a control for amiodarone, demonstrated that the hospitalization survival rate was 22.8% (41/180) in the amiodarone group, compared with the 12.0% (20/167) in the lidocaine group ($p=0.009$). However, despite the increased ROSC success and hospitalization survival rates, amiodarone could not improve the discharge survival rate compared with the placebo and lidocaine groups.

In this systematic review, not only the ROSC success rate but also the discharge survival rate was superior in the Japanese guideline group compared with the AHA guideline group. These findings provide new insight into the traditional AHA CPR guidelines.

4.3. Appropriate administration method of amiodarone

Some questions remain to be answered. In practice, the method of slow injection over 10 min is too slow for an emergency situation. How can we use amiodarone and achieve prompt results? Early defibrillation can be achieved by giving a rapid bolus injection with a high dose of amiodarone, and good recovery of brain function may also be expected. Meanwhile, PEA/asystole or severe bradycardia may be induced by such amiodarone administration procedures. Because amiodarone acts on multiple ion channels and thus decreases the excitability of ventricular myocardium and sinus node cells, such procedures could promote vascular dilatation and a negative inotropic effect, subsequently resulting in hypotension and shock. In such cases, the combined use of a catecholamine with amiodarone cannot be avoided. We would need to know the potential increase in the risk of VF

occurrence by catecholamine, for if VF were to be initiated again, there would be little hope of rescuing the patient.

The 8 reports summarized in this article provide insight as to the appropriate administration rate and amiodarone dose for CPR. However, a limitation of the present study was that the statistical analysis did not take into account multiple disease-related factors such as age, underlying disease, severity, bystander CPR, cardiac arrest interval, and adverse effects. It cannot be denied that the results might have been different if the data were subjected to a multivariate analysis. A larger number of cases is necessary to resolve this problem. For this purpose, a large-scale survey on CPR, the SOS-KANTO Study 2012, has already been in progress by the KANTO Region of Japanese Association for Acute Medicine (http://www.jaam-kanto.jp/about_sos_kanto.html). More than 15,000 CPA cases have already been banked in the center during the last year. The analyses of all these data warrant the establishment of important guidelines for the actual uses of amiodarone.

4.4. Limitations

For increasing the Japanese population in this study, not only original papers but also conference proceedings and abstracts were included. Thus, the quality of each article is a major problem, and careful interpretation is necessary for the meta-analysis, with a high statistical confidence level. Because the studies were not randomized trials and only few examinations were performed, a systematic review was adopted instead of a meta-analysis. The results of study 1 remain only for reference. From these findings, we could not conclude the superiority of amiodarone to nifekalant.

Conflict of interest

Amino et al. received no financial and personal relationship with other people or organizations.

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