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Original Article

Retrospective Analysis of the Safety of High-Volume Dental Articaine Preparations for Japanese Patients

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We retrospectively analyzed the safety of the use of articaine, an amide-type local anesthetic, in Japanese dental patients (n = 300) treated in Thailand in 2015-2017. The dosage, adverse events (AEs) caused by local anesthesia, and treatment efficacy were examined. Articaine, which is safe for patients with liver impairments due to its unique metabolism, has not been thoroughly tested in Japan for doses above 5.1 mL. Eighty of the present patients had undergone root canal treatment (RCT), 71 underwent tooth extraction, and 149 underwent implant-related surgery. More than three articaine cartridges were used in 41 patients, and no AEs occurred in these cases. The only AE occurred in a 52-year-old woman who was treated with three cartridges and presented with what appeared to be hyperventilation syndrome; she later recovered and received her dental treatment as scheduled. Most treatments were completed with three or fewer cartridges, suggesting that this number is generally sufficient. Our findings, particularly the low AE risk even with doses exceeding three cartridges, support the potential applicability of the overseas recommended maximum dose of articaine (7 mg/kg) in Japanese patients. This conclusion is significant for advancing dental anesthetic practices and ensuring patient safety and treatment efficacy in Japan.

Key words: dental anesthesia, local anesthesia, drug-related side effect, adverse reaction

The injectable local dental anesthetics approved in Japan are limited to lidocaine, prilocaine, and mepivacaine, with lidocaine formulations dominating the market. In other countries, articaine and bupivacaine are also available for dental use, providing a choice of nine combinations with vasoconstrictors in North America, for example [1]. Articaine, an amide-type local anesthetic, is metabolized not only in the liver but also by nonspecific esterase in the blood due to the presence of an ester bond in the structure. Articaine can be safely used in patients with impaired liver function.

In Japan, although a phase I trial of articaine began in 2016 and was followed by phase II and III trials [2-4], no clinical trials have been conducted in Japanese patients to determine the safety of higher doses exceeding three cartridges, *i.e.*, 5.1 mL of articaine. Our present investigation complements the clinicals trial in Japan. We retrospectively analyzed actual uses of artic-

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aine, the treatment completion, and adverse events caused by local anesthesia in Japanese patients who underwent dental treatment with articaine formulations in Thailand.

Patients and Methods

We gathered the cases of all of the consecutive Japanese patients aged ≥ 20 years who underwent dental treatment at the JP Green Dental Clinic in Bangkok, Thailand during the period from January 1, 2015, to June 29, 2017 and received an intraoral injection of an articaine formulation as a local anesthetic, until the planned number of cases (n = 300) was attained.

The following parameters were investigated. The study's primary endpoint was the treatment completion status. We examined the patients' age, gender, administration procedure (infiltration anesthesia alone or in combination with an inferior alveolar nerve block [IANB]), the number of cartridges of articaine formulation used, the total dose of the articaine formulation (mL), the number of patients receiving high doses (> 5.1 mL) of an articaine formulation, the number of teeth treated, the reason(s) for non-completion of treatment, the rescue use of other local anesthetics, and notable adverse events (AEs) during the treatment or within 7 days after the administration of the local anesthetic and the types of AEs. We also determined the presence of serious/non-serious AEs caused by local anesthesia during the treatment or within 7 days after the administration of the local anesthetic and the types of AEs.

The articaine formulation used for all of the patients consisted of 4% articaine with 1 : 100,000 adrenaline. Each IANB was performed with the conventional technique in which the needle is inserted into the pterygomandibular triangle from the direction of the contralateral mandibular premolar, keeping the needle parallel to the mandibular occlusal plane; the needle tip is advanced into the triangle and aspiration is conducted to rule out intravascular placement; the anesthetic is then injected in the triangle.

All root canal treatments (RCTs) were performed by a single endodontist. Similarly, all tooth extractions and implant-related procedures were conducted by one oral surgeon (A.P.). Both practitioners are experts in their respective fields, each possessing over 30 years of clinical experiences.

For the statistical analysis, we calculated descriptive statistics for continuous variables and calculated the frequencies and percentiles for categorical statistics. The cumulative distribution curves of the total doses of articaine were obtained. The study was approved by the Ethical Review Committees of Chulalongkorn University, Thailand (approval no. HREC-DCU 2022-069), Okayama University, Japan (approval no. Research2305-025), and Tokyo Medical and Dental University, Japan (approval no. D2022-079).

Results

As presented in Table 1, the study population consisted of 300 Japanese individuals (188 males and 112 females) aged 21-80 years (mean ± SD 48.4 ± 10.9 years). Table 2 lists the numbers of teeth treated in each treatment classification. Multiple treatments were relatively

Table 1 Distribution of patients by age and gender

		RCT	Teeth extraction		Implant-related operation	Total
			impacted	not impacted		
Age	Mean	43.6	45.7	47.2	51.6	48.4
	SD	10.5	16.7	8.3	10.8	10.9
	Minimum	21	30	33	24	21
	25 percentile	36.0	31.0	41.0	44.0	41.0
	Median	43.0	44.0	47.0	50.0	48.0
	75 percentile	48.5	49.0	51.0	59.0	55.0
	Maximum	66	76	66	80	80
Gender	Male (%)	39 (48.8%)	6 (100.0%)	43 (66.2%)	100 (67.1%)	188 (62.7%)
	Female (%)	41 (51.3%)	0	22 (33.8%)	49 (32.9%)	112 (37.3%)
	Total (n)	80	6	65	149	300

common among the patients who underwent implant treatment.

Infiltration anesthesia was performed in all 300 patients. As an addition, IANB was performed in 29 of the 80 cases of RCT, in all six cases of extraction of impacted teeth, in 37 of the 65 cases of extraction of not-impacted teeth, and in 90 of the 149 cases of implant-related surgery (Table 3).

The median volumes of articaine used were as follows: for the RCT group, 3.4 mL; for the extraction of impacted teeth, 5.1 mL; for the extraction of not-impacted teeth, 3.4 mL; and for implant-related surgery, 3.4 mL. A greater volume of articaine was used for the extraction of impacted teeth. Although the maximum volume used was 13.6 mL for implant-related surgery, the other volume quantiles were comparable to the extraction of not-impacted teeth (Table 4).

More than 5.1 mL of the articaine formulation (three cartridges) were used in 2 (2.5%) of the RCT cases, 2 (33.3%) of the extractions of impacted teeth, 11 (16.9%) of the extractions of not-impacted teeth, and 26 (17.4%) of the implant-related surgeries.

More than 6.8 mL of the articaine formulation (four cartridges) was used in 0 (0%) of the RCT cases, 0 (0%) of the extractions of impacted teeth, one (1.5%) of the extractions of not-impacted teeth, and six (4.0%) of the implant-related surgeries. (Table 5).

We analyzed the cases of the 41 patients who required high doses (exceeding three cartridges) of the articaine formulation. No AEs due to the articaine

Table 2 Number of teeth treated in each classification of treatment

	Number of teeth treated									
	1	2	3	4	5	6	7	8	9	Total
RCT	80	0	0	0	0	0	0	0	0	80
Teeth extraction (impacted)	5	1	0	0	0	0	0	0	0	6
Teeth extraction (not impacted)	52	11	1	0	0	0	0	1	0	65
Implant-related operation	96	37	8	5	0	0	0	2	1	149
Total	233	49	9	5	0	0	0	3	1	300

Table 3 Injection procedure in each classification of treatment

	Injection procedure		
	Infiltrate (n)	Infiltrate+block (n)	Total (n)
RCT	51	29	80
Teeth extraction (impacted)	0	6	6
Teeth extraction (not impacted)	28	37	65
Implant-related operation	59	90	149
Total	138	162	300

Table 4 Total dose of articaine used in each classification of treatment Unit : mL

	Average ± SD	Minimum	25 percentile	Median	75 percentile	Maximum	Cases (n)
RCT	2.86 ± 1.10	1.7	1.70	3.40	3.40	6.8	80
Teeth extraction (impacted)	5.24 ± 1.13	3.4	5.10	5.10	5.95	6.8	6
Teeth extraction (not impacted)	4.24 ± 1.58	1.7	3.40	3.40	5.10	8.5	65
Implant-related operation	4.43 ± 1.75	1.7	3.40	3.40	5.10	13.6	149
Total	3.98 ± 1.70	1.7	3.40	3.40	5.10	13.6	300

Table 5 Total doses and cumulative percentage of articaine used for each treatment

Amount (mL)		1.7	2.55	3.4	5.1	5.95	6.8	8.5	10.2	13.6	Total n	Mean
No. of cartridges		1	1.5	2	3	3.5	4	5	6	8	n	
Total	n	41	2	160	56	14	20	4	1	2	300	2.34
	cumulative %	13.7	14.3	67.7	86.3	91	97.7	99	99.3	100		
RCT	n	32	0	43	3	1	1	0	0	0	80	1.68
	cumulative %	40	40	93.8	97.5	98.8	100	100	100	100		
Teeth extraction (impacted)	n	0	0	1	3	1	1	0	0	0	6	2.49
	cumulative %	0	0	16.7	66.7	83.3	100	100	100	100		
Teeth extraction (not impacted)	n	8	1	26	19	3	7	1	0	0	65	3.08
	cumulative %	12.3	13.8	53.8	83.1	87.7	98.5	100	100	100		
Implant-related operation	n	1	1	90	31	9	11	3	1	2	149	2.6
	cumulative %	0.7	1.3	61.7	82.6	88.6	96	98	98.7	100		

injection were observed in these patients. In two patients' cases, the RCT of a single tooth was performed with doses of 6.8 and 5.95 mL, and IANB was also used. In one of these cases, the scheduled treatment for a molar with symptomatic apical periodontitis and a 5-mm periodontal pocket was not completed. The presence of active inflammation in this gingival condition likely attenuated the efficacy of the articaine, and the anatomical complexity due to the curvature of the pulp cavity further complicated the treatment. The incomplete RCT for this tooth was thus attributed to a combination of reduced effectiveness of articaine in the inflammatory state and the inherent difficulty of the RCT procedure itself.

Of the two cases in which impacted teeth were extracted, one involved a single mandibular impacted wisdom tooth and the other involved both mandibular and maxillary right wisdom teeth. Among the 11 cases of the extraction of not-impacted teeth, IANB was add in 10 cases. The remaining 26 cases were implant-related surgeries, with the highest dose at 13.6 mL used in two cases, followed by 10.2 mL in one case. The number of teeth treated in these patients was eight or nine. Among the 26 cases, IANB was combined in 24 (Table 6).

Of the total of 300 patients, the planned dental treatments were completed successfully in 287 patients (95.7%). All 13 cases in which the dental treatment could not be completed were related to RCT (Table 7). In all but one case in which 6.8 mL of articaine was used, the total amount of articaine was ≤ 3.4 mL (Table 8).

Four AEs were observed in a single patient, a 52-year-old female who received 5.1 mL of infiltration anesthesia of articaine in the anterior maxilla. She experienced difficulty breathing, restlessness, heavy sweating, and tachycardia shortly after the injection but soon recovered, and the planned treatment was completed. These AEs were judged as moderate in degree and non-serious side effects.

Discussion

Phase I through phase III clinical trials of articaine have been completed in Japan, confirming its safety and efficacy. However, there is insufficient evidence regarding the safety of articaine at high doses exceeding three cartridges. To supplement the clinical trials, we investigated the frequency and nature of adverse events in Japanese subjects living overseas, using their past medical records. We analyzed the cases of all 300 Japanese patients who received dental treatment using articaine cartridges in a dental clinic Thailand during the years 2015-2017, *i.e.*, before the coronavirus disease 2019 (COVID-19) pandemic. The occurrence of adverse events, the dosage, the treatment completion status, and other factors were collected from the patients' medical records. The patients' average (median) age in this study was 48.4 (48.0) years, which is close to the age 46.7 (46.7) years in Japan's 2015 population census.

We observed that more than three cartridges of the

Table 6 Description of patients more than 5.1 mL of articaine was used (n = 41)

Age	Sex	Treatment	Nerve block	No. of cartridges	Amount (mL)	No. of teeth treated	Complete
65	M	RCT	+block	4	6.8	1	No
44	M	RCT	+block	3.5	5.95	1	Yes
43	M	Ext (im)	+block	4	6.8	2	Yes
30	M	Ext (im)	+block	3.5	5.95	1	Yes
65	M	Ext	+block	5	8.5	8	Yes
45	M	Ext	+block	4	6.8	2	Yes
42	M	Ext	+block	4	6.8	1	Yes
35	F	Ext	no block	4	6.8	2	Yes
66	M	Ext	+block	4	6.8	2	Yes
50	F	Ext	+block	4	6.8	2	Yes
33	F	Ext	+block	4	6.8	1	Yes
39	M	Ext	+block	4	6.8	1	Yes
50	M	Ext	+block	3.5	5.95	1	Yes
36	F	Ext	+block	3.5	5.95	3	Yes
48	F	Ext	+block	3.5	5.95	1	Yes
58	F	Imp	+block	8	13.6	8	Yes
59	M	Imp	+block	8	13.6	8	Yes
44	M	Imp	+block	6	10.2	9	Yes
44	M	Imp	+block	5	8.5	4	Yes
80	F	Imp	+block	5	8.5	4	Yes
55	M	Imp	+block	5	8.5	4	Yes
80	F	Imp	+block	4	6.8	4	Yes
73	M	Imp	+block	4	6.8	3	Yes
52	M	Imp	+block	4	6.8	2	Yes
65	M	Imp	+block	4	6.8	2	Yes
35	F	Imp	no block	4	6.8	2	Yes
51	M	Imp	+block	4	6.8	2	Yes
65	M	Imp	+block	4	6.8	4	Yes
65	M	Imp	+block	4	6.8	3	Yes
65	M	Imp	+block	4	6.8	2	Yes
51	M	Imp	no block	4	6.8	2	Yes
33	F	Imp	+block	4	6.8	1	Yes
64	F	Imp	+block	3.5	5.95	2	Yes
24	F	Imp	+block	3.5	5.95	2	Yes
40	M	Imp	+block	3.5	5.95	2	Yes
64	F	Imp	+block	3.5	5.95	2	Yes
50	M	Imp	+block	3.5	5.95	1	Yes
45	M	Imp	+block	3.5	5.95	3	Yes
49	F	Imp	+block	3.5	5.95	2	Yes
48	F	Imp	+block	3.5	5.95	1	Yes
50	M	Imp	+block	3.5	5.95	3	Yes

RCT, root canal treatment; Ext, tooth extraction; im, impacted tooth; +block, combination of infiltration and block anesthesia; no block, infiltration anesthesia with no block anesthesia.

articaine formulation were used in 41 of the total of 300 patients and in 15 of the 151 cases excluding those of implant-related treatment. Thus, 90.1% of the dental treatments including extractions and excluding implant-related surgery were performed with three cartridges, suggesting that three cartridges is generally sufficient for effective anesthesia in routine dental procedures for Japanese patients. More than four cartridges were used in only one of these 151 cases. In that patient's case, five cartridges were used for the extraction of eight not-impacted teeth. It is therefore apparent that four cartridges can provide the required dosage in common dental treatments. A phase III confirmatory study was conducted in Japan concerning the

Table 7 Number of cases planned treatment could not be completed

	Total	RCT	Teeth extraction		Implant-related operation
			impacted	not impacted	
Completed	287 (95.7%)	67 (83.8%)	6 (100%)	65 (100%)	149 (100%)
Not completed	13 (4.3%)	13 (16.3%)	0	0	0
Total	300	80	6	65	149

Table 8 Cases planned treatment could not be completed (n = 13)

Age	Sex	Treatment	Nerve block	No. of cartridges	Amount (mL)	No. of teeth treated
65	M	RCT	+block	4	6.8	1
40	M	RCT	+block	2	3.4	1
47	F	RCT	+block	2	3.4	1
49	F	RCT	no block	2	3.4	1
48	F	RCT	+block	2	3.4	1
42	F	RCT	+block	2	3.4	1
44	M	RCT	+block	2	3.4	1
48	F	RCT	no block	1	1.7	1
31	F	RCT	no block	1	1.7	1
39	M	RCT	no block	1	1.7	1
31	F	RCT	no block	1	1.7	1
59	F	RCT	no block	1	1.7	1
61	F	RCT	no block	1	1.7	1

extraction of an impacted wisdom tooth with the starting dose of two or three cartridges of articaine. When additional doses were required during treatment, up to a total of four cartridges were allowed, but only one of the study's 42 patients received an additional dose, for a total of four cartridges [4].

In our present analyses, the planned treatment was not completed in 13 cases, all of which were RCTs. Root canal treatment is inherently time-consuming, and it is standard practice to reschedule this treatment for completion at a subsequent appointment if it exceeds the allotted time. The use of IANB may explain why all 13 cases with incomplete treatment were RCTs. Among the 13 cases, only two required more than two cartridges of articaine, and just one of these cases remained incomplete. This incompletion can be attributed to the combination of the patient's inflammatory gingival condition and the inherent difficulty of performing RCT on this treatment tooth.

In many countries, the maximum recommended dose for articaine in healthy adults is 7 mg/kg [5]. Among the present study's patients, eight cartridges (544 mg) were used as the maximum dose for one male and one female patient, and no adverse events were observed. This dose corresponds to 7.8 or 9.1 mg/kg in an adult weighing 70 or 60 kg. Although the safety of up to three cartridges of articaine has been evaluated in clinical trials in Japan [2-4], no ethnicity-specific issues have been reported for local anesthetics, and the application of the overseas maximum recommended dose of articaine for Japanese patients seems reasonable. We thus speculate that the maximum recommended dose of articaine for healthy Japanese adults could be 7 mg/kg, like the overseas recommendation.

Based on the results of this study, we inferred that even with the use of articaine exceeding three cartridges, adverse events were not immediately triggered in Japanese adults. We suspect that the likelihood of immediate adverse events due to the use of more than three articaine cartridges is low even in elderly patients. However, although we included all of the consecutive cases described above, other local anesthetics might be

used or the treatment plan might be changed to avoid using local anesthesia in some cases. For elderly patients and those with serious circulatory disorders or allergies, the risk of adverse events may be higher, necessitating an appropriate evaluation before treatment and monitoring during treatment.

The only adverse event recorded in this study was mild, in a 52-year-old female. Although hyperventilation syndrome was suspected in her case based on the recorded symptoms, this syndrome is one of the most commonly observed discomfort symptoms after the administration of local anesthetics in dental practice [6]. Moreover, since adrenaline is added to articaine at a concentration of 1 : 100,000, tachycardia is a very common pharmacological effect of adrenaline, and this patient's case does not suggest any compromise in the safety of articaine. Moreover, 52 years was slightly higher than the average age of the study population, and no trend was observed indicating an increase in the incidence of adverse events with age in these Japanese adults. A limitation of this study is that the dentists' experience and treatment procedures were not standardized, as this was a retrospective observational study. These factors may have affected the number of cartridges used and/or the decision-making about changes in the treatment plan in the RCT cases, but they do not appear to have affected the rate of adverse events since only a mild adverse event was observed in one case of the total of 300 cases.

Together the results of this study demonstrate that three cartridges of an articaine formulation safely exerted sufficient efficacy in routine dental treatments including extractions for Japanese adults. Additional doses were also safe. The likelihood of adverse events occurring even with doses exceeding three cartridges was found to be very low. Our findings also suggested that the maximum recommended dose of articaine for healthy Japanese adults could be 7 mg/kg, as is used overseas.

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