

Smell Intensity Monitoring Using Metal Oxide Semiconductor Odor Sensors during Intravenous Olfaction Test

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Abstract

The intravenous olfaction test using prosultiamine (PST) solution is simple to perform and has been used clinically in Japan. We monitored intranasal intensity of smell continuously in real time under various conditions of administration using metal oxide semiconductor odor sensors and established an optimal PST injection procedure. In this study, we found that 1) although there was fluctuation in the pattern of intensity of increase in smell in the PST original solution test, the pattern of increase in intranasal smell intensity could be stabilized by prolonging the injection time to 40 s and 2) dilution of PST with physiological saline was effective in preventing angialgia during intravenous injection. It appears that PST administration is best performed by adding 10 ml of saline to 10 mg (2 ml) of PST and injecting the resulting 12-ml solution (6× dilution) and that the best respiratory cycle for testing is once in every 2 s.

Key words: intranasal smell intensity, intravenous olfaction test, metal oxide semiconductor odor sensor, Portable Odor Meter, prosultiamine

Introduction

The intravenous olfaction (IVO) test is a clinical olfaction test and has been widely used in Japan. The latent time from injection of prosultiamine (PST) to recognition of smell and the duration time between recognition and disappearance of smell were measured after intravenous injection of PST. The mechanism of IVO is believed to be retronasal olfaction of the odorous exhalation after intravenous administration of odorous substance. However, neither how PST when injected intravenously circulates through the body nor how amounts of odorous substance in the nasal cavity change over time is fully understood. Kazama and Zusho (1981) reported the amount of propyl mercaptan (metabolite of PST) in expired air during the IVO test, but their findings were based on intermittent measurements at intervals of 20–30 s and not on continuous measurement. Based on Kazama's study, it has been thought that during the IVO test, the amount of propyl mercaptan peaks only once in intensity and then gradually decreases. However, patients sometimes perceive that PST odor (which is garliclike) decreases once and then increases again repeatedly, suggest-

ing the possibility of repeated peaks of propyl mercaptan during the IVO test. In this study, we monitored intranasal smell intensity continuously in real time under various conditions of administration using metal oxide semiconductor odor sensors, a kind of artificial nose, and established an optimal PST injection procedure.

Materials and methods

The subjects were 20 male and 5 female healthy volunteers without olfactory disturbance, aged 24–37 years with a mean \pm standard deviation (SD) of 29.7 ± 3.3 . Ten milligrams (2 ml) of PST (Alinamin, Takeda, Osaka, Japan) was administered intravenously into the right median cubital vein. The subjects were instructed to close their eyes and raise their left hand when they perceived garliclike smell and when the smell disappeared. Latent times between initiation of PST solution injection and recognition of garliclike smell and durations of smell were measured. During the IVO test, smell intensity was measured by metal oxide semiconductor

odor sensors (Portable Odor Meter, Futaba Electronics, Yokohama, Japan) (Figure 1). The system has two sensors that are sensitive to light-odor substances such as alcohol and heavy-odor substances such as toluene. Two sensor outputs were expressed on the rectangular coordinates as odor vectors. These vectors were synthesized, and the smell intensity was expressed as the length of the vector. Intranasal air samples were collected using a 12-Fr suction catheter located near the olfactory cleavage at intervals of 0.5 s, and intranasal smell intensity was measured. It has been reported that smell intensity measured with this sensor is significantly correlated with odorous substance concentration (Murakami *et al.*, 2003). Intravenous administration of PST solution was performed as follows: the total amount of PST solution injected was the same (10 mg) in all the following groups. Group 1: injection of PST (10 mg/2 ml) over a period of 20 s ($n = 10$), according to the standard protocol for the IVO test (Takagi, 1989). Group 2: injection of PST over 5 s ($n = 5$). Group 3: injection of 2 \times -diluted solution of PST with saline (4 ml) over 40 s ($n = 5$). Group 4: injection of PST over a period of 20 s and subsequent flushing with 10 ml of saline ($n = 5$). Group 5: injection of 4 \times -diluted solution of PST with saline (total 8 ml) over 40 s ($n = 5$). Group 6: injection of 6 \times -diluted solution of PST with saline (total 12 ml) over 40 s ($n = 5$). Group 7: injection with 8 \times -diluted solution of PST with saline (total 16 ml) over 40 s ($n = 5$). Group 8: injection as for Group 3 and subsequent flushing with 10 ml of saline ($n = 5$). Group 9: injection as for Group 5 and subsequent flushing with 10 ml of saline ($n = 5$). Group 10: injection as for Group 6 and subsequent flushing with 10 ml of saline ($n = 5$). Group 11: injection as for Group 7 and subsequent flushing with 10 ml of saline ($n = 5$). Group 12: injection of PST over 10 s ($n = 5$).

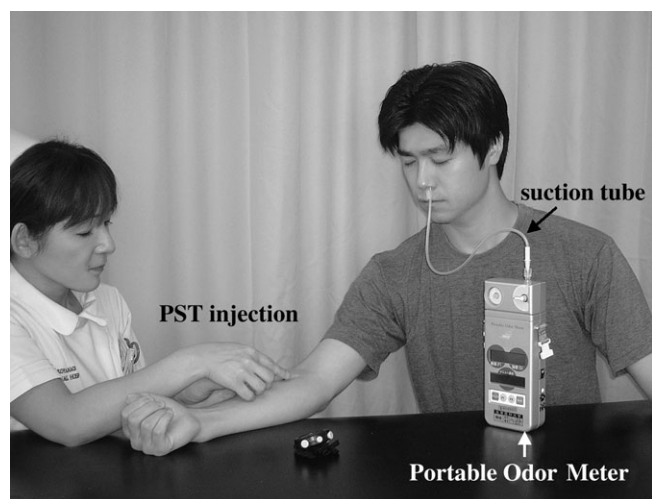


Figure 1 This is a scene of the PST injection and the measurement procedure. The Portable Odor Meter is a device for measurement of intensity of smell with two metal oxide semiconductor odor sensors. It is 88 \times 250 \times 43 mm in size and weighs 780 g. The front end of the odor suction tube is located near the olfactory cleavage.

In Groups 1–4, subjects were studied with resting nasal breathing once every 4 s (inspiration: 2 s and expiration: 2 s), while in Groups 5–12, subjects were studied with resting nasal breathing once every 2 s (inspiration: 1 s and expiration: 1 s). In addition, in Groups 1, 3, 6, and 12, the subjective intensity of smell and the extent of angialgia were examined and classified using an 11-rank visual analogue scale (VAS) from 0 to 10. No odor and no pain were designated 0, while the maximum possible intensities of smell and of angialgia were designated 10. The pH values of the 2 \times - to 8 \times -diluted PST solutions were measured using an analytical instrument (Digital pH meter HM30V, DKK-TOA Corp., Tokyo, Japan).

Results

Results (mean \pm SD) for latent time, duration of smell, and increase in smell intensity in Groups 1 through 11 are summarized in Table 1. Figure 2 is a graph showing the change in smell intensity following PST injection over 20 s. The intensity of smell in samples withdrawn from the nasal cavity increased during expiration and decreased during inspiration along the curved line. The time when the subjects perceived the garliclike smell was identical to the duration of increase in intensity of smell during expiration. In 7 of 10 cases, the intensity peaked once and then gradually decreased (Figure 2a). Subjective PST odor intensity also peaked and then gradually decreased in synchrony with change in the measured smell intensity. In 3 of 10 cases, however, subjects perceived that PST odor intensity decreased once and increased again after the first cessation of smell. The smell intensity peaked and then gradually decreased, followed by repeated lower intensity peaks and gradual decreases in intensity (Figure 2b). When the intensity peaks emerged again, the subjects also perceived increases in PST odor. In the group in which a total of 4 ml of 2 \times -diluted PST solution was injected intravenously over 40 s, all subjects exhibited the single-peak

Table 1 IVO test parameters in each group

	Latent time (s)	Duration time (s)	Increase in smell intensity
Group 1	10.5 \pm 1.8	109.8 \pm 14.9	973.6 \pm 343.5
Group 2	8.8 \pm 0.6	100 \pm 11.4	1065 \pm 190.6
Group 3	12.7 \pm 1.3	126 \pm 11.5	569.8 \pm 156.8
Group 4	10.2 \pm 0.6	120.6 \pm 8.4	1030.8 \pm 111.2
Group 5	10.9 \pm 1.1	127 \pm 10.2	587.8 \pm 154.8
Group 6	11.0 \pm 1.1	129.6 \pm 7.5	633 \pm 52.0
Group 7	11.2 \pm 0.9	124.6 \pm 9.6	465.2 \pm 84.2
Group 8	10.8 \pm 1.1	126.6 \pm 8.6	528.4 \pm 250.5
Group 9	11.0 \pm 1.1	128.6 \pm 6.4	608.2 \pm 176.9
Group 10	10.8 \pm 1.2	126.8 \pm 4.9	662.6 \pm 215.1
Group 11	11.9 \pm 1.1	121.8 \pm 7.8	408 \pm 76.3

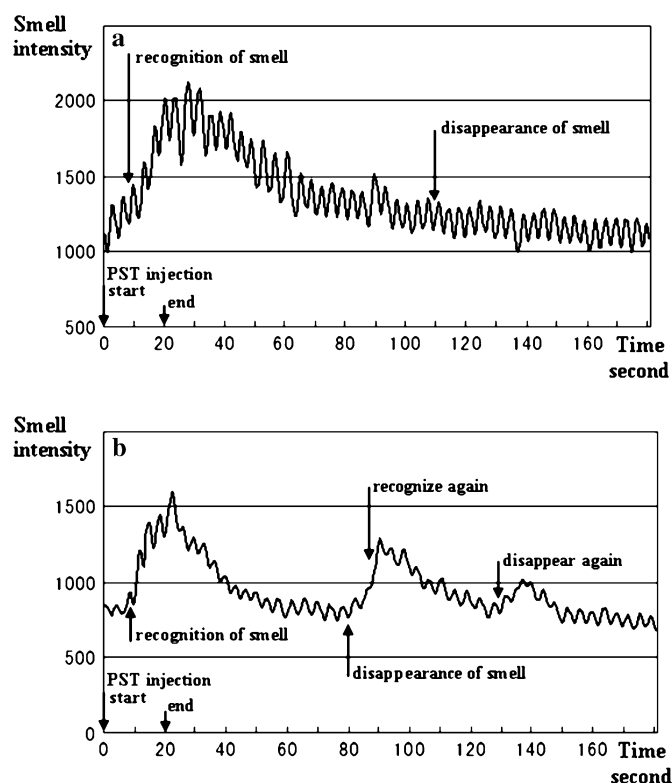


Figure 2 (a) Smell intensity curves with PST injection (2 ml) over 20 s. The ordinate represents smell intensity and the abscissa the time from intravenous injection. In 7 of 10 cases, intensity peaked once and then gradually decreased. The subject is a 30-year-old male having a single-peak intensity pattern. (b) In 3 of 10 cases, smell intensity peaked and then gradually decreased, followed by repeated lower intensity peaks and gradual decreases in intensity. This graph shows a repeated-peak intensity pattern taken from a 28-year-old female.

pattern. Because the PST solution was injected over a longer period, the latent time was longer and the increase in intensity was less than that with injection over 20 s (Table 1). All the subjects who received 4×, 6×, or 8× dilution over 40 s exhibited the single-peak pattern. As seen in Figure 3, as the total amount of injection increased from 4 to 12 ml, both duration of smell and intensity slightly tended to increase. But when the subjects received a total of 16 ml injection, both duration and intensity tended to decrease. These increases and decreases were both not significant statistically [repeated-measures analysis of variance (ANOVA)]. Comparison between groups with and without flushing with 10 ml of saline after PST injection revealed that postinjection flushing tended to extend duration of smell slightly when a smaller amount of PST solution (total amount of injection of 4–8 ml) was injected, although advantageous effects were not observed with 6× and higher dilutions (total amount of injection of 12–16 ml). There was no significant change in duration extension by saline flushing (repeated-measures ANOVA).

When the subjects underwent injection of the original solution of PST over 20 s, subjective smell intensity score was

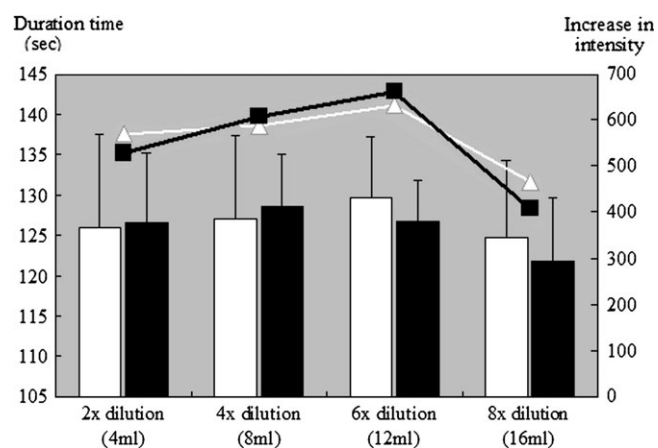


Figure 3 Duration and intensity of smell in four conditions of IVO testing over 40 s. Filled columns show duration of smell without flushing of 10 ml of saline after PST injection. Open columns show duration of smell with flushing. Open triangles show increase in intensity without flushing. Filled squares show increase in intensity with flushing. Error bars show SDs.

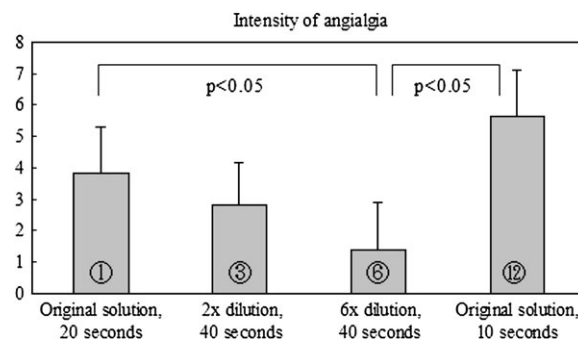


Figure 4 Angialgia scores for four sets of IVO test conditions. Error bars show SDs. Scores with 6×-diluted injection over 40 s were significantly lower than with injection of the original solution over 10 or 20 s ($P < 0.05$, repeated-measures ANOVA).

7.0 ± 1.4 (mean \pm SD). Subjects who received PST injection over 40 s in the form of 2× dilution had the lowest subjective smell intensity, in the range of 5–8 with a mean \pm SD of 6.0 ± 1.2 . Subjective smell intensity in the group injected with 6×-diluted solution over 40 s was 6.8 ± 1.9 . That in the group injected with the original solution of PST within 10 s was highest and ranged from 5 to 9 with a mean \pm SD of 7.4 ± 1.8 . There were no significant differences in subjective smell intensity among these four groups. The VAS scores for angialgia when PSTs were injected as original solution over 20 s, 2× dilution over 40 s, and 6× dilution over 40 s were 3.8 ± 1.5 (mean \pm SD), 2.8 ± 1.3 , and 1.4 ± 1.5 , respectively (Figure 4). When PSTs were injected as original solution over 10 s, the angialgia score was highest and it was 5.6 ± 1.5 (mean \pm SD). There was a significant difference in angialgia score between the group injected with 6× dilution over 40 s and that injected with the original solution over 20 s or 10 s (repeated-measures ANOVA, $P < 0.05$).

The pH values of the original solution, 2× dilution, 4× dilution, 6× dilution, and 8× dilution of PST, and physiological saline were 3.5–3.76, 5.61–5.65, 6.12–6.15, 6.24–6.26, 6.35–6.36, and 6.38–6.41, respectively.

Discussion

The report on the occurrence of smell sensation following intravenous neosalvarsan injection by Forchheimer (1916) was the first related to the effects on olfaction of intravenous drug injection, and Ueda (1957) reported the IVO test using PST in 1957. Since then, the IVO test has been widely used in Japan, and olfactory disturbance undetectable with the IVO test was reported to be associated with poor clinical outcome (Zusho *et al.*, 1980). The latent and duration times in the IVO test have been believed not always to be correlated with clinical outcome (Zusho *et al.*, 1980), but this lack of correlation may be the result of inconsistency of olfactory stimuli in the original IVO test. Kazama and Zusho (1981) reported amounts of PST metabolites in expired air during the IVO test as determined by gas chromatography, and their results have been accepted as standard values. Based on their findings, it has been believed that PST metabolite concentration has single peak in time course. However, in their study, expired air samples were collected at intervals of 20–30 s from only four subjects, and expired air was not analyzed continuously; thus, they did not accurately monitor changes over time in amounts of odorous substance. In the present study, changes in intranasal intensity of smell were monitored at intervals of 0.5 s using an artificial nose, and findings demonstrated the existence of two patterns of change in the amount of odorous substance. We therefore suggest that the test procedure and method of evaluation of results of the IVO test hitherto used should be revised.

When PST was injected over 20 s (original IVO test), the latency and duration times were similar to normal values reported elsewhere (Takagi, 1989). Although seven subjects in this group exhibited a single-peak intensity pattern, three exhibited a repeated-peak intensity pattern. These three subjects reported repetitive smell sensation during the test. Ishimaru *et al.* (2004) also reported that repetition of smell was occasionally observed in IVO test. Emergence of repeated intensity peaks may be explained as follows. 1) First, the effects of reperfusion of PST administered by bolus injection. More subjects exhibited the repeated-peak intensity pattern than the single-peak intensity pattern when PST was injected over 5 s, probably because bolus injection is more likely to cause disequilibrium in the distribution of PST in the blood. 2) Second, the possibility that PST remaining stagnant in the veins enters the pulmonary circulation later. In dye-dilution method using indocyanine green (ICG) for measuring liver function, the dye remains stagnant in the veins, and Oda (1979) noted that it is therefore necessary to flush with 5–10 ml of a suitable solution after ICG injection. In addition, mixing of such a reagent in the right ven-

tricle was reported to be unexpectedly inefficient (Oda, 1979), and the reagent may be trapped in the veins or remain stagnant in the right atrium or right ventricle even after intravenous PST injection. Intensity peaks may thus reemerge when PST stagnant in the veins enters the pulmonary circulation later. Because such repeated emergence should affect evaluation of duration, conditions yielding single-peak intensity pattern are essential for generation of stable olfactory stimuli. When PST was administered not by bolus injection but over an extended period of time, 40 s, all subjects exhibited the single-peak intensity pattern.

When PST was injected over 40 s with subsequent flushing with 10 ml of saline, the duration of smell was longer than that with the PST original solution test. This might have been due to stagnation of PST behind venous valves. In addition, the finding that flushing with additional saline was effective in reducing fluctuation in duration suggests that prevention of venous stagnation of PST should be effective in obtaining stable olfactory stimuli. In addition, a 2-s respiratory cycle resulted in a latent time shorter than that with a 4-s cycle. Because odor is sensed only during expiration, a longer inspiration phase or odor-insensitive period appeared to cause an error of 1–2 s. These findings indicate that a 2-s respiratory cycle is suitable for evaluation of latent time. When the drug was injected over 40 s, a single intensity peak was observed in all 40 trials and PST odor was sensed only once. This finding suggests that injection of PST over a period of 40 s is suitable for generating reproducible and uniform olfactory stimuli. A period of about 50 s is required for the blood to circulate through the entire body at rest (Goto, 1979). On the other hand, 23 s is the minimum time for a substance injected intravenously to return to the site of injection (Goto, 1979). Therefore, if a substance is injected for 20 s, substance-free blood will flow for several seconds at the injection site just after the injection procedure is completed. In attempting to make the blood distribution of the substance more uniform, it would thus be reasonable to inject the substance in 36.5 s, which is a middle time point between 50 and 23 s.

Duration and increase in intensity both increased as the amount of injection volume increased from 4 ml (2× dilution) to 12 ml (6× dilution) but decreased at 16 ml (8× dilution). Further, when the amount of injection was smaller (2–4 ml), postinjection flushing was effective in prolonging the duration to some extent, but this advantageous effect was not observed in the groups with 6× and higher dilutions (12–16 ml). Although increase in injection volume appears to be effective in preventing stagnation of the substance in the veins, 8× or higher dilution may result in attenuation of odor. In addition, given its simplicity, PST injection would best be performed with 6× dilution with saline (addition of 10 ml of saline to 2 ml of PST).

It has been reported that 45% of tested subjects complained of vascular pain during IVO test, and this pain was due to the leakage of PST solution having a strong acidity (pH 3.5)

(Hatanaka *et al.*, 2004). However, no effective prevention has been taken for this important side effect.

Dilution of the original solution of PST with saline resulted in simultaneous shift of pH toward neutrality, mitigating the angialgia that occurred during testing with the PST original solution due to acidity. Since administration of 6×-diluted solution yielded almost the same results for subjective odor intensity as the original method, PST injection with 10 ml physiological saline addition over 40 s can be recommended for use as a new IVO test. The correlations between latent time and duration of smell determined with consistent olfactory stimuli using the new 6× dilution IVO test and clinical outcomes will be reevaluated in clinical studies in the near future.

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Accepted November 2, 2005