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SPECIAL ARTICLE

History of T-cain: a local anesthetic developed and manufactured in Japan

Masaru Tobe[1] · **Shigeru Saito**[2]

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Abstract In many anesthesia textbooks written in English, lidocaine, tetracaine, bupivacaine, ropivacaine, and chloroprocaine are listed as useful local anesthetics for spinal anesthesia. In contrast, T-cain is not included in these lists, even though it has been reported to be suitable for spinal anesthesia in Japan. T-cain was developed as a local anesthetic in the early 1940s by Teikoku Kagaku Sangyo Inc. in Itami, Japan, by replacing a methyl group on tetracaine (Pantocaine®) with an ethyl group. T-cain was clinically approved for topical use in Japan in November 1949, and a mixture of dibucaine and T-cain (Neo-Percamin S®) was approved for spinal use in May 1950. Simply because of a lack of foreign marketing strategy, T-cain has never attracted global attention as a local anesthetic. However, in Japan, T-cain has been used topically or intrathecally (as Neo-Percamin S®) for more than 60 years. Other than the side effects generally known for all local anesthetics, serious side effects have not been reported for T-cain. In fact, several articles have reported that T-cain decreases the neurotoxicity of dibucaine. In this historical review, the characteristics of T-cain and its rise to become a major spinal anesthetic in Japan are discussed.

Keywords Local anesthetic · T-cain · Dibucaine · Spinal anesthesia · Topical anesthesia

✉ Masaru Tobe
to-be@f3.dion.ne.jp

[1] Intensive Care Unit, Gunma University Hospital, 3-39-22, Showa, Maebashi, Gunma 371-8511, Japan

[2] Department of Anesthesiology, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

Introduction

We reviewed the history of local anesthetic agents and the unique background, history, and fate of T-cain. T-cain was developed and used for spinal anesthesia in combination with dibucain in Japan for more than 50 years, and it faded away in the 2010s.

Development of local anesthetics: from cocaine to modern enantiometric agents

The history of local anesthetics originates from the finding of the analgesic effect of coca leaves, which were commonly used medicinally in South America. Although the effect had been described in the fifteenth to sixteenth centuries, the first clinical use of cocaine for operative anesthesia was in 1884 by Carl Koller, who used it in an ophthalmologic operation. The use of cocaine for spinal anesthesia was first reported by Karl Gustav August Bier in 1898 [1, 2].

Cocaine was an outstanding drug as the first local anesthetic; however, it also had many deficits, such as difficulty of sterilization, short duration of effect, and addiction after repeated use. Amylocaine was thus developed in 1903 and used for spinal anesthesia; however, its use was interrupted because of associated irritability. Then, procaine was developed in 1905 by Alfred Einhorn [1], working for Hoechst AG, and was shown to have low toxicity, acceptable chemical stability, and no addictive properties. Procaine replaced cocaine in many clinical applications.

Dibucaine was developed in 1929, and tetracaine was developed in 1928 by Eisler [3]. Although dibucaine had relatively high neurotoxicity, it was reported to be suitable for spinal anesthesia and thus started to be used widely for

surgery. Tetracaine was used clinically from 1932 and also introduced for spinal anesthesia. However, because of its chemical instability after solubilization, its use was relatively limited and it did not replace dibucaine. The development of T-cain from tetracaine partly overcame the deficits of tetracaine; however, as described next, the use of T-cain was limited to Japan, where it had been developed.

The synthesis of lidocaine by Nils Lofgren and Bengt Lundqvist in 1942 was epoch making because of its chemical stability, clinical safety, and local infiltrative property. Following the clinical introduction of lidocaine in 1944, released by Astra Company in 1948, the usage of previous local anesthetics dramatically decreased. Further pharmaceutical development of lidocaine derivatives resulted in mepivacaine (1957: approximate year of initial clinical use in "reference 1"), prilocaine (1960), bupivacaine (1963), ropivacaine (1996), and levo-bupivacaine (1998) [3, 4]. These relatively new local anesthetics share many pharmaceutical and pharmacological characteristics. However, they have different durations of action, degrees of cardiac toxicity, and local infiltrative properties. Therefore, physicians choose the most suitable one depending on the intended type of anesthesia, whether spinal, epidural, topical, or local infiltrative.

Development of T-cain

In March 1942, Kazuo Nakajima (Fig. 1a) of Teikoku Kagaku Sangyo Inc. developed a new local anesthetic, T-cain. T-cain was prepared by replacing a methyl group (CH_3) on tetracaine (Pantocain) with an ethyl group (C_2H_5), and its chemical name is 2-(diethylamino)ethyl *p*-(buthylamino)benzoate hydrochloride (Fig. 2). Because of the similarity in their chemical formulae, the pharmacological characteristics of T-cain and tetracaine are also similar. Teikoku Kagaku Sangyo Inc. originated from Rinkei-ya, which was a dye and paste manufacturer founded in 1832 by Denbei Nagase (Fig. 1b). In 1938, Teikoku Kagaku Sangyo Inc. was founded as an affiliated company of the Nagase group, responding to a request from the Japanese government to make chemical products domestically. At that time, there were two different backgrounds behind the need of new local anesthetic in Japan: first, as a clinical issue as most surgical procedures were performed under regional anesthesia and there was room for improvement in preexisting local anesthetics, and second, political and diplomatic conflicts between Japan and other countries, which had resulted in World War II, would have been a threat to the international trade of medical products. Teikoku Kagaku Sangyo Inc. first produced dibucaine, which was the most modern and standard local anesthetic at the time, for domestic use, with the commercial name

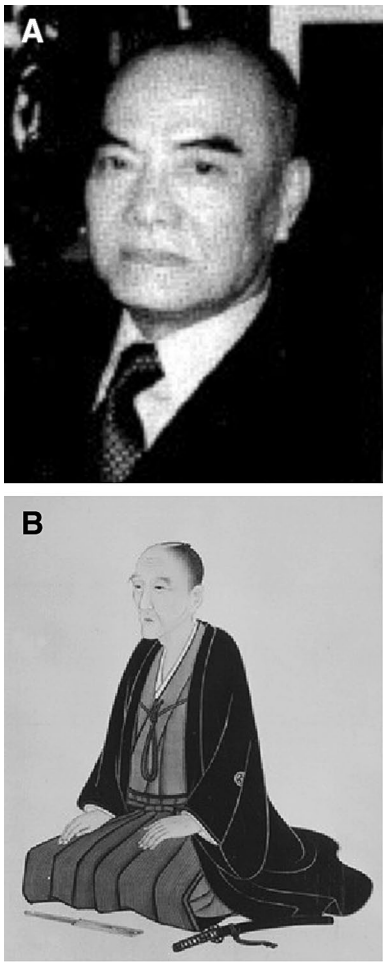

Fig. 1 **a** Photograph of Kazuo Nakajima, who invented T-cain. In March 1942, Kazuo Nakajima of Teikoku Kagaku Sangyo Inc. developed a new local anesthetic, T-cain. **b** Photograph of Denbei Nagase, the founder of Rinkei-ya. Denbei Nagase and the founder of Rinkei-ya, which later became Teikoku Kagaku Sangyo, Inc.

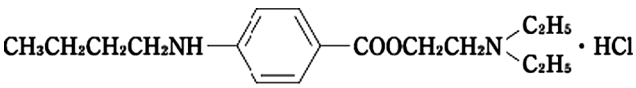

Fig. 2 Chemical formula of T-cain

Percamin. Kazuo Nakajima, a chemist at Teikoku Kagaku Sangyo Inc., developed T-cain. The company investigated and manufactured many combinations of T-cain, dibucaine, chloroprocaine, and vasoconstrictive drugs (Table 1) [5].

In 1942, Saito reported a pharmaceutical manufacturing method for T-cain and its clinical effects in 24 cases of abdominal or leg surgery under spinal anesthesia [6]. In particular, he examined the effects of the inclination of the patients when receiving a spinal injection of T-cain, and the onset time of analgesia was reported to be 2–3 min. Goto and Nishimura tested topical effects of T-cain on the

Table 1 History of T-cain

1832: Denbei Nagase opened a dye and paste shop in Kyoto called Rinkei-ya. His business gradually expanded, and Rinkei-ya became a chemical company, Nagase Inc., in 1917
1938: The chemical division of Nagase Inc. was founded as Teikoku Kagaku Sangyo Inc. (Imperial Chemistry Inc.)
1941: Dibucaine manufactured in Japan was released as Percamin®
1942: T-cain was developed by Kazuo Nakajima by modifying the tetracaine molecule
1942: Saito reported a pharmaceutical manufacturing method for T-cain and clinical effects in 24 cases under spinal anesthesia
1943: The topical effects of T-cain were reported by Shuji Goto
1950: A mixture of dibucaine and T-cain, Neo-Percamin S®, was commercially released for spinal use
1972: Nagase Medicals Inc. was reestablished by combining Teikoku-Kagaku Sangyo Inc. and the pharmaceutical division of Nagase Sangyo Inc.
2000: Initiation of shipping of 0.5 % bupivacaine for spinal use in Japan
2013: Termination of manufacturing and shipping of Neo-Percamin S®

rabbit cornea and human nasal mucosa [7]. In particular, they examined 51 otorhinolaryngeal cases and concluded that T-cain was safer than cocaine and had vasoconstrictive properties.

Kan and Kawano described that T-cain was more potent than tetracaine in rabbits [8]. They examined its topical effects on the cornea, its cardiovascular effects (toxicity) when intravenously injected, and its intestinal effects when used on isolated bowel specimens, and they found that T-cain had a longer effect than tetracaine, did not induce local irritation, and had a wider therapeutic margin than cocaine. T-cain has central nervous toxicity, as observed for other local anesthetics; however, rescue by respiratory and circulatory support was easier than in the case of other anesthetics. The onset of pharmacological action of T-cain is faster than that of dibucaine. Therefore, Yuasa recommended that T-cain should be mixed with dibucaine, which was the most widely used local anesthetic at that time, for spinal and topical (especially dental) anesthesia [9]. He also examined the effect of subcutaneous injection of T-cain on human skin sensation, antihistaminic effects in the guinea pig bronchus, and cardiovascular and anticonvulsant effects upon intravenous injection in rabbits. Although the duration of pharmacological action for T-cain was relatively long, its metabolism and elimination from blood appeared to be rapid [8]. This relatively rapid elimination, similar to that of tetracaine, was reconfirmed in 1975 by Otsuka and Furuta in rodents [10].

Additionally, Ishiyama, Fujino, and Masuda of Kyushu University reported the effects of T-cain applied to the lingual tip of human volunteers [11]. They compared the analgesic effect of T-cain with that of cocaine and dibucaine, and concluded that T-cain was a nearly perfect local anesthetic because it was easy to prepare, stable after preparation, potent for analgesia, and effective for a long duration.

Following the aforementioned basic studies, T-cain use was clinically approved as a local infiltrative in November 1942, and Neo-Percamin S (a mixture of dibucaine and T-cain) was approved in May 1950 for spinal use. However, these preparations of T-cain were not shipped outside Japan. Simply because of a lack of foreign marketing strategy, T-cain has never attracted global attention as a local anesthetic.

T-cain for spinal anesthesia

Introduction of T-cain for spinal anesthesia

At that time, tetracaine was used under the name of Pantocain in Japan or Pontocaine in the United States (USA). Neo-Percamin was the registered name of the mixture of dibucaine and T-cain prepared for spinal anesthesia by Teikoku Kagaku Sangyo Inc. [9]. The use of T-cain for spinal anesthesia could have been approved very quickly with very limited clinical experience at that time, in contrast to the present situation.

T-cain for spinal use was only prepared in a mixture with dibucaine because dibucaine was widely used in spinal anesthesia as a standard local anesthetic at that time. The purpose of adding T-cain was to shorten the onset time of spinal anesthesia. The independent effects of T-cain during spinal use are not generally known.

Pharmacological features of T-cain for spinal anesthesia

Some T-cain-containing solutions were clinically released for spinal anesthesia (Table 2). Hypobaric Neo-Percamin contained 0.2 % T-cain, 0.3 % dibucaine, and 0.5 % NaCl; isobaric Neo-Percamin contained 0.2 % T-cain, 0.3 % dibucaine, and 0.7 % NaCl. Neo-Percamin S, clinically used much longer, contained 0.12 % T-cain, 0.24 % dibucaine, and 9.5 % glucose. Kitahara et al. composed several mixtures of local anesthetics, such as dibucaine, T-cain, tropacocaine, tetracaine, and salt or glucose, and examined the effects of these mixtures in spinal use [12].

Table 2 Clinically released T-cain-containing solutions

For spinal anesthesia	
Hypobaric Neo-Percamin® (1951–1970)	0.2 % T-cain, 0.3 % dibucaine, 0.5 % NaCl
Isobaric Neo-Percamin® (1950–1970)	0.2 % T-cain, 0.3 % dibucaine, 0.7 % NaCl
Neo-Percamin S® (1950–2013) (from 1950 to 1953, Neo-Percamin S® contained 5.0 % NaCl rather than 9.5 % glucose)	0.12 % T-cain, 0.24 % dibucaine, 9.5 % glucose
For local and topical anesthesia	
0.1 % T-cain: (1942–1964) (local infiltration or conduction anesthesia)	0.1 % T-cain
0.2 % T-cain (1942–1964) (dental conduction anesthesia)	0.2 % T-cain
0.5 % T-cain (1963–1974) (topical anesthesia)	0.5 % T-cain
Anecain® (1950–1971) (dental local anesthesia)	0.2 % T-cain, 0.1 % dibucaine
Rocain® (1952–1964) (infiltration, conduction, and topical anesthesia)	0.2 % T-cain, 0.05 % dibucaine, 2.0 % adrenaline solution
Paiocain-T.E (tecrocain)® (containing 1:100,000 adrenaline) (1964–1974) (infiltration and conduction anesthesia)	0.2 % T-cain, 1.5 % chloroprocaine, 0.2 % glucose

They found that hyperbaric Neo-Percamin, which contained 0.24 % dibucaine, 0.12 % T-cain, and 9.5 % glucose, was the most suitable mixture for spinal anesthesia.

Mori experimentally examined the effect of various T-cain concentrations by asking the manufacturer to prepare a spinally usable T-cain solution and then administering this solution in 40 clinical cases [13]. Mori concluded that 1 % T-cain was the most suitable local anesthetic for spinal use and also found that when T-cain was combined with dibucaine, the onset time of spinal anesthesia and the neurotoxicity of dibucaine were reduced.

Repeated spinal injection of the mixture of Neo-Percamin through an intrathecal catheter was also reported by Honda et al. in 1952 [14], when they modified the repeated tetracaine injection method introduced by Saklad et al. [15] and concluded that this method could be safely used for segmental anesthesia. Kato examined a mixture of 0.2 % T-cain and 0.3 % dibucaine in 24 gynecological spinal anesthesia cases and demonstrated that this combination induced a faster onset and longer effective duration than dibucaine solution administered alone and also that side effects such as headache and nausea were minor [16]. Neo-Percamin S, used until recently, contained 0.12 % T-cain, 0.24 % dubucaine, and 9.5 % glucose. The pH of Neo-Percamin S is 4.0–5.0, and its specific gravity is 1.035–1.039.

Adverse events during spinal anesthesia using Neo-Percamin S

Sakai et al. considered that reducing the amount of spinally injected dibucaine should be beneficial to decrease serious neurological side effects and thus tried to determine the lowest dose of Neo-Percamin S necessary for spinal anesthesia [17]. They examined 315 cases of abdominal and leg surgery and concluded that less than 1.5 ml Neo-percamin S, which contained 0.12 % T-cain and 0.24 % dibucaine in a glucose solution with a specific gravity of 1.037 at 15 °C, was sufficient to obtain appropriate analgesia. He injected the local anesthetic solution with the patient's head angled down 5°; the patients were instructed to maintain this head position for 3–4 min after injection.

Fukui studied the adsorption and distribution of local anesthetics in rabbit spinal cords and human cadaver spinal cords, and demonstrated that the adsorption of T-cain in the spinal cord was higher than that of tetracaine and lower than that of dibucaine [18]. He also suggested that because the adsorption of T-cain was relatively rapid, the anesthetized area could be fixed relatively quickly after the spinal injection. Such early fixation of the effective area was considered to decrease the likelihood of unexpected high spinal blockade.

The side effects reported for spinal use of Neo-Percamin S were hypotension, bradycardia, respiratory arrest, and allergy. However, these side effects are commonly observed for all local anesthetics and were thus considered not to be specific for this combination. Because T-cain was rarely used for spinal anesthesia as a single drug, its specific side effects have not been reported. Matsuki reviewed spinal anesthesia-related deaths in Japan and identified a notable number of deaths associated with the use of Neo-Percamin S for spinal anesthesia [19]; most of these deaths were considered to be incurred by inappropriate management of hypotension and respiratory arrest during high spinal anesthesia.

Because reports of cardiopulmonary arrest following spinal anesthesia were more common among patients of younger age, Hirabayashi and Shimizu studied the spread of spinally injected local anesthetic in the lower extremity or lower abdominal surgeries [20]. They reported that hyperbaric Neo-Percamin S tended to produce an unexpectedly extensive spread of anesthesia in young patients.

Fate of spinal T-cain

Saeki et al. surveyed the most commonly used local anesthetics for spinal anesthesia in three university hospitals in Tokyo during the month of November 1995 [21]. At that time, dibucaine, Neo-Percamin S, tetracaine, and lidocaine were clinically available in Japan. In that study, a total of 140 spinal anesthesia procedures was surveyed. Of these procedures, dibucaine was used in 43.6 % and Neo-Percamin S was used in 35.7 %. Unexpectedly, Saeki found unauthorized use of bupivacaine in 16.4 % of cases. In such unauthorized use, bupivacaine prepared for peripheral or epidural use, which contained preservatives such as methylparaben and propylparaben, was utilized (peripheral and epidural bupivacaine use was authorized in 1969 in Japan). Other than side effects commonly observed for spinal anesthesia, such as hypotension, bradycardia, and nausea, no serious drug-specific side effects were observed in this survey.

Although bupivacaine was reported to be safer than dibucaine for spinal anesthesia, governmental approval for spinal use of bupivacaine was extremely delayed in Japan. Because spinal administration had already been established in the USA and Europe following the development of bupivacaine in 1963, unauthorized spinal use spread rapidly in Japan. Considering this medicosocial situation, in July 1997 the Japanese Society of Anesthesiologists urged the Ministry of Health, Labor, and Welfare of Japan to expedite its bureaucratic authorization of the spinal use of bupivacaine. Finally, in 2000, the use of bupivacaine for spinal anesthesia was authorized in Japan. This delay of almost 40 years prolonged the use of Neo-Percamin S for spinal anesthesia in Japan.

Ester-type local anesthetics are well known to induce a higher rate of allergic reactions than amide anesthetics [1]. Additionally, direct neurotoxicity of dibucaine was widely announced in the late 1990s [2]. For these reasons, the use of dibucaine in spinal anesthesia has been diminishing, and dibucaine has now been mostly replaced by bupivacaine for spinal use. Because T-cain is used in a mixture with dibucaine, the use of T-cain has also been diminishing simultaneously (Fig. 3). As a result, Teikoku Kagaku Sangyo Inc. decided to terminate the manufacturing and shipping of Neo-Percamin® for spinal use in 2012.

T-cain for nonspinal anesthesia

T-cain was also used topically in Japan, especially in the field of ophthalmology. For topical use, a simple T-cain solution (i.e., not mixed with dibucaine) was prepared for clinical application. Nishioka examined the effect of topical T-cain on human volunteers and patients after he studied its effect on the rabbit cornea [22]. On

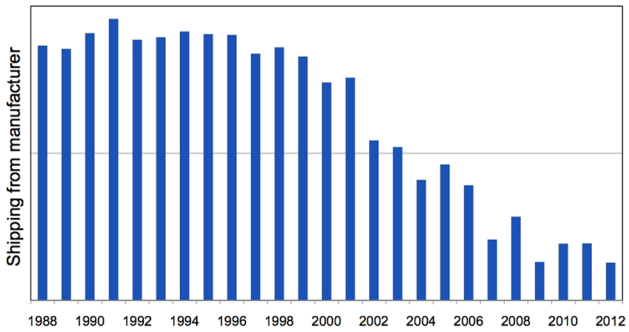

Fig. 3 Ample amounts of Neo-PercaminS®. Decreased shipping of dibucaine and T-cain mixture, Neo-Percamin S®. Shipping of Neo-Percamin S® from the manufacturer decreased greatly after 2000, which marked the start of authorized use of 0.5 % bupivacaine for spinal anesthesia. The actual amounts shipped are confidential and were not disclosed by the manufacturer

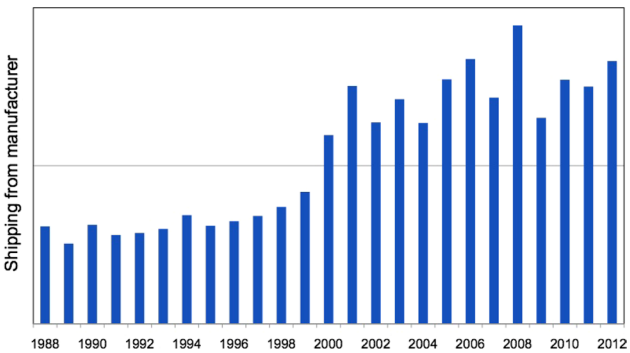

Fig. 4 Sales amount (g) of T-cain. Increased shipping of T-cain for topical use. Shipping of topical T-cain from the manufacturer has increased because of expanded use for tympanic topical anesthesia. The actual amounts shipped are confidential and were not disclosed by the manufacturer

the rabbit cornea, the effect was apparent at 19.6 s after topical application, and the effect lasted for 66 min on average. No irritation was observed when topical T-cain was applied to healthy volunteers, and it was found to be effective in 60 patients (81 eyes) with only minimal and temporary side effects (such as conjunctive redness). In contrast, Kaneko compared seven local anesthetics and found that 0.2 % topical T-cain produced slight corneal irritation in human eyes and 0.3 % produced moderate corneal irritation [23].

Koshinaga surveyed 63 cases of anesthesia-related death reported from 1948 to 1958 in Tokyo and found that 5 deaths occurred after topical use of T-cain, although a causative relationship could not be identified [24].

A mixture of 0.2 % T-cain and 0.1 % dibucaine was also produced for dental use as Anecain by Teikoku Kagaku Sangyo Inc., and a mixture of 0.2 % T-cain, 1.5 % chloroprocaine, 0.2 % glucose, and 1:100000 adrenaline was

produced for nonspinal local anesthesia as Techlocain (later renamed Paiocain-T.E.) (Table 2).

In contrast, the use of T-cain for topical and/or infiltrative use has been expanding in otorhynolaryngology and ophthalmology. According to information from Teikoku Kagaku Sangyo Inc., T-cain is now widely used for topical anesthesia of the tympanic membrane (Fig. 4). Several different formulations for in-hospital pharmacy preparation have also been reported [25].

Conclusion

T-cain was the most frequently used local anesthetic for spinal anesthesia in Japan in the 1940s–1960s, as prepared in a mixture with dibucaine. However, the market for spinally administered T-cain is almost ended. For spinal anesthesia, Neo-Percamin has been almost completely replaced by 0.5 % bupivacaine. However, T-cain is still used for topical/infiltrative anesthesia in some specialties. T-cain may also be used as an alternative in patients who are allergic to lidocaine or bupivacaine. T-cain is still used only in Japan because of the lack of a global marketing incentive. Anesthesiologists should continue to be aware of the existence of this unique local anesthetic.

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References

1. Strichartz GR, Berde CB. Local anesthetics. In: Miller RD, editor. Miller's anesthesia. 6th ed. Philadelphia: Elsevier; 2005. p. 573–603.
2. McLure HA, Rubin AP. Review of local anaesthetic agents. Minerva Anestesiol. 2005;71:59–74.
3. Ruetsch YA, Boni T, Borgeat A. From cocaine to ropivacaine: the history of local anesthetic drugs. Curr Top Med Chem. 2001;1:175–82.
4. Whiteside JB, Wildsmith JA. Developments in local anaesthetic drugs. Br J Anaesth. 2001;87:27–35.
5. Fujita T, Matsuki A. Nippon Masuikagakushi Shiryou (The history of Japanese Anesthesiology) (in Japanese). Tokyo: Kokuseido; 1987.
6. Saito M. Spinal anesthesia with hyperbaric T-cain (in Japanese). Nippon Gekagakkai Zasshi (J Jpn Surg Soc). 1942;43:773–7.
7. Goto S, Nishimura N. Analgesic effect of T-cain when applied on mucous surface (in Japanese). Chiryou Shohou. 1943;24:697–700.
8. Kan B, Kawano K. A new local anesthetic, T-cain (in Japanese). Jicchiikarinsho. 1944;21:115–21.
9. Yuasa Y. Certain pharmacological properties of T-cain (in Japanese). J Yonago Med Assoc. 1955;6:135–9.
10. Otsuka M, Furuta H. Acute toxicity in mice, rats and rabbits and its concentration and hydrolysis in the rabbit's plasma of *p*-buthylaminobenzoyl diethylamino ethanol hydrochloride (in Japanese). Oyo Yakuri (Pharmacometrics). 1975;9:413–20.
11. Ishiyama F, Fujino H, Masuda T. Clinical study of Japan made local anesthetic, T-cain (in Japanese). Lecture summary of Rinsho-geka Ikai, pp 1–11 [unknown date (in Nagase Inc. archives)]
12. Kitahara T, Matsubara J. Kakushu sekimazai no yakkou wo chuusinntosite (Pharmacological effects of several local anesthetics prepared for intrathecal use (in Japanese). Shujyutsu. 1955;9:42–7.
13. Mori S. Neo-percamin as a local anesthetic for spinal anesthesia. A research focusing on T-cain (in Japanese with English abstract). Masui (Jpn J Anesthesiol). 1956;5:273–9.
14. Honda K, Katami J, Hiroki F. The segmental anesthesia technique (in Japanese with English abstract). Masui (Jpn J Anesthesiol). 1952;1:104–9.
15. Saklad M, Dwyer CS, Kronenberg S, Neves E, Sorkin M. Intraspinal segmental anesthesia; a preliminary report. Anesthesiology. 1947;8(3):270–87.
16. Kato T. Neopercamin S siyouseiseki (report of cases where Neo-percamin S was used for anesthesia) (in Japanese). Rinsho-Fujinka-Sanka. 1954;8:43–7.
17. Sakai T, Shimizu I, Seki K, Yoneyama N, Ito H. Spinal anesthesia with several small amounts of Neo-percamin S solution (in Japanese with English abstract). Masui (Jpn J Anesthesiol). 1962;11:477–82.
18. Fukui M. A legal medicine study on lumbar spinal anesthesia (in Japanese). Nippon Houigaku Gakkai Zasshi (Legal Med). 1970;24(2):136–58.
19. Matsuki A. Spinal anesthesia related death in Japan (in Japanese). Tokyo: Kokuseido; 1999.
20. Hirabayashi Y, Shimizu R. The spread of spinal anesthesia in young patients (in Japanese with English abstract). Masui (Jpn J Anesthesiol). 1993;42:1274–7.
21. Saeki S, Suzuki H, Ogawa S, Hanaoka K, Kugimiya T, Yokoyama K, Isshiki J, Hosoyamada A, Kikuchi H. A clinical pharmacology surveillance of Neo-percamin S (in Japanese). Shinyaku to Rinshou (J New Remedies & Clinics). 1997;46:1721–34.
22. Nishioka K. The effects of Nittencain® when topically used on eyes (in Japanese). Jpn Rev Clin Opthalmol. 1973;67:249–53.
23. Kaneko R. Comparison of several different types of local anesthetics when topically used on eyes (in Japanese). Jpn Rev Clin Opthalmol. 1957;51:743–9.
24. Koshinaga J, Ide K, Nezu T, Hagiwara H. On sudden deaths subsequent to anesthesia in the past decades since the opening of the medical examiner's office (in Japanese). Nippon Daigaku Igakuzasshi. 1959;18:1250.
25. Japanese Society of Hospital Pharmacists. Byoin Yakkyokuseizai Jireishu (List of in-hospital pharmacy preparations) (in Japanese). Tokyo: Yakujinippousha; 2013.