LanbotulinumtoxinA (LAN)

Subjects: Others
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LanbotulinumtoxinA (LAN) was introduced in China. It is now available in Asia, Latin America and Eastern Europe under various brand names including Hengli®, Lantox®, Prosigne®, Lanzox®, Redux®, Liftox®, HBTX-A and CBTX-A.

Keywords: botulinum toxin ; therapy ; Chinese botulinum toxin ; lanbotulinumtoxinA

1. Introduction

Botulinum toxin (BT) is produced by the anaerobic bacterium Clostridium botulinum. In the early 19th century, Justinus Kerner first recognised BT as the cause of botulism. In 1980, Alan B. Scott invented BT's therapeutic use by applying it as a muscle relaxant for the treatment of strabismus in children [1]. In the meantime, BT's use has expanded tremendously into numerous therapeutic indications and into widespread aesthetic use.

In China, the development of therapeutic BT started in 1985 by Professor Yinchun Wang at the Lanzhou Institute of Biological Products. Wang was trained by Edward J. Schantz at the University of Wisconsin in botulism research. In 1993, his product was approved by the Ministry of Health of the People's Republic of China. This made China—after the USA and the UK—the third country in the world producing therapeutic BT. In 1997, the Lanzhou product was licensed by the Chinese Food and Drug Administration under the name lanbotulinumtoxinA (LAN, Lantox®; Lanzhou Institute of Biological Products, Lanzhou, China) as a drug for the treatment of strabismus, blepharospasm and hemifacial spasm. In 2012, this license was extended to moderate to severe glabellar frown lines. In 2002, LAN was successfully registered in South Korea. Since then, it has spread over Asia, Latin America and Eastern Europe, including major countries such as Brazil, India, Mexico and Russia [2]. LAN is available under various brand names such as Hengli®, Prosigne®, Lantox®, Lazox®, Redux®, Liftox®, HBTX-A and CBTX-A. In this entry, we will use LAN as the abbreviation of the generic name lanbotulinumtoxinA.

2. LanbotulinumtoxinA (LAN)

2.1. Motor Indications

2.1.1. Dystonia

Dystonia was—after strabismus and together with hemifacial spasm—the second group of indications developed. It is still the largest indication group for BT's therapeutic use. Publications on blepharospasm also include the treatment of Meige syndrome, hemifacial spasm and sometimes cervical dystonia.

Table 1 shows two randomised controlled trials on LAN in blepharospasm. One of them [3] showed no difference in efficacy and safety between LAN and ONA. The other one [4] showed that sparing the medial lower eyelid improves tear film stability and lacrimal fluid drainage. One cross-over interventional study [5] found no difference in efficacy and safety between LAN and ONA.

Table 1. LAN publications on dystonia and hemifacial spasm.

Authors	I	D	n	Methods	Results
Quagliato et al. [3]	BS HFS	RCT	57	Comparing LAN and ONA. BS = 21, HFS = 36. LAN = 29, ONA = 28. LAN dose: ONA dose ratio = 1:1. Total BS dose: 60 MU. Total HFS dose: 35 MU	No differences in efficacy and AE
Lu et al. [4]	BS	RCT	85	Comparing traditional injection sites and injection sites sparing medial lower eyelids	Sparing medial lower eyelids improves tear film stability and lacrimal fluid drainage

Authors	I	D	n	Methods	Results
Rieder et al. [5]	BS HFS	IS	26	Comparing LAN and ONA. Cross-over design. BS = 8, HFS = 18. LAN dose:ONA dose ratio = 1:1. Total dose: 2.5–5 MU per injection site	No differences in efficacy and AE
Peng et al. [6]	HFS	RCT	63	Comparing effects of traditional injection sites and those of traditional injection sites with an additional dose of 4 MU in posterior auricular muscle (PAM). HFS with auricular symptoms	Additional PAM injections reduce auricular symptoms
Li et al. [7]	HFS	IS	20	Comparing LAN with a dose of 50 MU/mL and LAN with a dose of 25 MU/mL. Cross-over design. LAN dose: 2.5–5 MU in each injection site. Washout period: 12 months	No difference in efficacy. Longer duration and more AE with higher LAN concentration
Barbosa et al. [2]	CD	RCT	34	Comparing LAN and ABO. ABO = 14. LAN = 20. ABO dose:LAN dose ratio = 3:1. Follow-up for 5 injection series every 3 months.	No difference in efficacy, effect duration and AE
Quagliato et al. [8]	CD	RCT	24	Comparing LAN and ONA. LAN dose–ONA dose ratio = 1:1. Total dose: 300 MU	No difference in efficacy, effect duration and AE
Huang et al. [9]	CD	RCT	105	Comparing oral drugs, LAN and LAN with orthopaedic joint brace (external fixator for head, neck, chest and back). Ultrasound guidance	LAN with orthopaedic joint brace is better than LAN alone. Oral medication without efficacy
Wu et al. [10]	CD	RCT	68	Comparing LAN with EMG guidance and LAN without EMG guidance.	EMG guidance with prolonged efficacy and less AE, but more injection site pain. Maximal efficacies are not different.
Hu et al. [11]	CD	RCT	126	Comparing LAN with a dose of25 MU/mL and LAN with a dose of 17 MU/mL	No difference in efficacy and AE
Luo et al. [12]	CD	RCT	27	Comparing LAN with a dose of 50 MU/mL and LAN with a dose of 12.5 MU/mL	No difference in efficacy and AE
Hu et al. [13]	SD-AD	RCT	27	Comparing LAN with a dose of 5 MU and LAN with a dose of 10 MU. Blitzer grade: ≥III. Blitzer dose: 25 MU/mL. EMG guidance. Unilateral thyroarytenoid injections	No difference in onset time, time-to-peak effect and AE. Higher dose produces a longer effect duration
Jiang & You [14]	TMJD	RCT	90	Comparing semiconductor laser treatment and semiconductor laser treatment with LAN injection	Semiconductor laser therapy with LAN has a better efficacy on inflammation and pain than semiconductor laser treatment alone.

I, indication; D, design; n, number of patients/controls; RCT, randomised controlled trial; BS, blepharospasm; HFS, hemifacial spasm; CD, cervical dystonia; SD-AD, spasmodic dysphonia (adductor type); IS, interventional study; AE, adverse effects; LAN, Lantox®; TMJD, temporomandibular joint dysoorder.

Table 1 shows six selected randomised controlled trials for cervical dystonia. One study [8] compared LAN and ONA at a 1:1 dose conversion ratio, and one study [2] compared LAN and ABO at a 1:3 dose conversion ratio. Both studies did not find a difference in efficacy and safety between both drugs. One study [9] showed that LAN together with orthopaedic joint braces has a better efficacy than LAN alone, whereas oral drugs are not effective.

Table 1 shows the randomised controlled trial on adductor-type spasmodic dysphonia [13]. It was demonstrated that LAN with a dose of 10 MU produces longer effects than LAN with dose of 5 MU whereas peak efficacy and safety of these two doses are not different.

Table 1 shows the randomised controlled trial on temporomandibular joint disorders [14]. It was demonstrated that semiconductor laser therapy with LAN has better efficacy on inflammation and pain than semiconductor laser therapy alone.

2.1.2. Hemifacial Spasm

Table 1 shows two randomised controlled trials and two interventional studies on LAN for hemifacial spasm, one randomised controlled trial [3] and one interventional study [5] by comparing LAN and ONA, and no difference in efficacy and safety was found when converted on a LAN and ONA dose conversion ratio of 1:1. One randomised controlled trial [6]

showed additional posterior auricular muscle injections can reduce acoustic symptoms, and one interventional study [7] showed that the LAN dose of 50 MU/mL produces longer therapeutic effects and more adverse effects than that of 25 MU/mL whereas the peak efficacies at these two doses are identical.

2.1.3. Tics

Tics have been tried successfully on several occasions, because of their similarity with dystonia, especially cranial dystonia (Table 1).

Table 2. Overview over all lanbotulinumtoxinA (LAN) publications retrieved from Pubmed and Science and Technology Paper Citation Database.

Motor Indications									
Indication	**S**	**PT**	**ST**	**All**	**RCT**	**IS**	**OS**	**CS**	**RG**
Blepharospasm	**N**	**32**	**3**	**35**	**2**	**6**	**27**		
Meige syndrome	**N**	**13**	**4**	**17**		**1**	**15**	**1**	
Cervical dystonia	**N**	**32**	**0**	**32**	**7**	**1**	**24**		
Craniocervical dystonia	**N**	**5**	**0**	**5**		**1**	**4**		
Writer's cramp	**N**	**2**	**0**	**2**			**2**		
Dystonias	**N**	**11**	**1**	**12**			**12**		
Spasmodic dysphonia	**E**	**3**	**0**	**3**	**1**		**2**		
TMJ disorder	**N**	**3**	**0**	**3**	**1**		**2**		
Hemifacial spasm	**N**	**17**	**18**	**35**	**2**	**3**	**30**		
Tics	**N**	**1**	**0**	**1**			**1**		
Spasticity	**N**	**40**	**0**	**40**	**18**	**7**	**14**	**1**	
Cerebral Palsy	**P**	**38**	**0**	**38**	**16**	**7**	**15**		
Strabismus	**O**	**17**	**1**	**18**	**1**	**2**	**15**		
Bladder dysfunction	**U**	**8**	**0**	**8**	**3**	**1**	**4**		
Gastroparesis	**G**	**1**	**0**	**1**				**1**	
Achalasia	**G**	**2**	**0**	**2**				**2**	
Oesophageal strictures	**G**	**1**	**0**	**1**	**1**				
Dysphagia	**G**	**1**	**0**	**1**				**1**	
Anismus	**S**	**1**	**0**	**1**			**1**		
Raynaud syndrome	**N**	**1**	**0**	**1**				**1**	
Tinnitus	**E**	**1**	**0**	**1**				**1**	
Glandular indications									
Hyperhidrosis	**N**	**11**	**0**	**11**	**2**	**2**	**7**		
Sialorhea	**N**	**4**	**0**	**4**	**1**		**3**		
Prostate hyperplasia	**U**	**1**	**0**	**1**				**1**	
Pain indications									
Migraine	**N**	**20**	**0**	**20**	**7**	**2**	**11**		
Trigeminal neuralgia	**N**	**9**	**0**	**9**	**3**	**2**	**3**	**1**	
Postherpetic neuralgia	**N**	**3**	**0**	**3**	**1**		**1**	**1**	
Aesthetic indications									
Wrinkles	**A**	**36**	**1**	**37**	**5**	**2**	**30**		

Motor Indications									
Indication	**S**	**PT**	**ST**	**All**	**RCT**	**IS**	**OS**	**CS**	**RG**
Calf reduction	**A**	**6**	**0**	**6**		**1**	**5**		
Masseter reduction	**A**	**2**	**0**	**2**			**2**		
Scars	**A**	**2**	**0**	**2**			**1**	**1**	
Acne	**A**	**1**	**0**	**1**				**1**	
Methods									
Drug comparison		**3**	**0**	**3**		**2**	**1**		
Remote effects		**1**	**0**	**1**		**1**			
Allergic reactions		**2**	**0**	**2**				**2**	
Reviews and guidelines									
Reviews									**18**
Guidelines									**2**
All		**351**	**28**	**379**	**71**	**41**	**232**	**15**	**20**

S, medical specialty (A, aesthetics; E, ear, nose and throat; G, gastroenterology; N, neurology; O, ophthalmology; P, paediatrics; S, surgery; U, urology; PT, primary topic publication; ST, secondary topic publication; All, all publications; RCT, randomised controlled trial; IS, interventional study; OS, observational study; CS, case study; R, review; G, guideline; TMJ, temporomandibular joint.

2.1.4. Spasticity

Spasticity is another main indication for BT therapy. Historically, it was developed after strabismus, dystonia and hemifacial spasm. As shown in Table 2, 40 LAN publications (all as primary topic publications) refer to spasticity.

2.1.5. Cerebral Palsy

Cerebral palsy is a syndrome consisting of various neurologic deficits all caused by perinatal brain damage. Motor deficits are the hallmark, frequently including dystonic and spastic elements which have been treated successfully with BT therapy for many years. Economically, cerebral palsy turns out to be one of the most important BT indications, not only because of its prevalence, but also because of the usually high BT doses applied. As shown in Table 2, 38 LAN publications refer to the treatment of cerebral palsy, all as primary topics.

2.1.6. Strabismus

Strabismus is the first indication developed by Alan B. Scott for BT therapy. One randomised controlled trial [15] showed that LAN injections with sodium hyaluronate have identical efficacy as LAN injections alone, but produce less ptosis.

2.1.7. Bladder Dysfunction

Table 3 shows three randomised controlled trials on bladder dysfunctons. One of them [16] showed that LAN is more effective in female overactive bladder than oral drugs, and one [17] showed that LAN with a dose of 200 MU including the trigonum and LAN with a dose of 300 MU excluding the trigonum produce identical efficacy and safety.

Table 3. LAN publications on bladder dysfunctions.

Authors	I	D	n	Methods	Results
Li et al. [16]	**OB**	**RCT**	**24**	**Comparing LAN with a dose of 100 MU and oral drugs. Only females. Target muscle: detrusor excluding trigonum**	**LAN is more effective.**
Fu et al. [17]	**NI**	**RCT**	**60**	**Comparing LAN with a dose of 200 MU including trigone and LAN with a dose of 300 MU excluding trigonum. Follow-up at 4 weeks**	**No difference in efficacy and AE**
Meng et al. [18]	**NB**	**RCT**	**35**	**Comparing a LAN dose of 200 MU with electro-acupuncture and LAN alone. Transperineal application into external urethral sphincter**	**Combined therapy is more effective.**

I, indication; D, design; n, number of patients/controls; RCT, randomised controlled trial; AE, adverse effects; LAN, Lantox®; OB, overactive bladder; NI, neurogenic Incontinence; NB, neurogenic bladder.

2.1.8. Gastroenterological Indications

Gastroenterological indications are a collection of mainly experimental indications with achalasia being the most robust one studied. As shown in Table 2, altogether five LAN publications refer to gastroenterological indications. One publication as a primary topic covers gastroparesis, two publications are about achalasia (both as primary topic publications), one publication is about oesophageal strictures (as a primary topic publication) and one publication is about dysphagia (as a primary topic publication).

2.2. Glandular Indications

2.2.1. Hyperhidrosis

As shown in Table 4, two randomised controlled trials on axillary hyperhidrosisone of them [19] demonstrated that LAN with a dose of 200 MU per axilla has longer efficacy than LAN with a dose of 50 MU per axilla. The other randomised controlled trial [20] suggested that LAN is more effective for mild and moderate axillary hyperhidrosis, whereas surgical gland excision is more effective for severe one.

Table 4. LAN publications on glandular indications.

Author	I	D	n	Methods	Results
Gao et al. [19]	**AH**	**RCT**	**92**	**Comparing LAN with a dose of 200 MU and LAN with a dose of 50 MU**	**A higher LAN dose has a longer efficacy.**
Xie et al. [20]	**BH**	**RCT**	**150**	**Comparing LAN and surgical gland excision**	**LAN is more effective for mild and moderate BH and less effective for severe BH.**
Peng et al. [21]	**S**	**RCT**	**98**	**Comparing LAN with electrical stimulation and electrical stimulation alone**	**Combination therapy is more effective than electrical stimulation.**
Ding et al. [22]	**BPH**	**OS**	**32**	**LAN with a dose of 200 MU was injected into five points at the lateral and middle lobes of the prostate under the guidance of ultrasound with a balloon dilatational device.**	**All symptoms and indicators are improved and maintained for a period of at least 1 year.**

I, indication; D, design; n, number of patients/subjects; RCT, randomised controlled trials; AE, adverse effects; LAN, Lantox®; AH, axillar hyperhidrosis; S, sialorhea; BH, bromhidrosis; BPH, benign prostatic hyperplasia.

2.2.2. Sialorrhea

As shown in Table 4, one randomised controlled trial [21] showed that the electrical stimulation of tongue, orbicular oris and buccinators muscles with LAN is more effective than electrical stimulation alone.

2.3.3. Prostate Hyperplasia

As shown in Table 4, one observational study [22] suggested the effect of LAN on benign prostate hyperplasia. The mechanism involved remains unclear.

2.4. Pain Indications

Pain indications are indications where the therapeutic effect is based upon modulations of nociception, pain transmission and pain processing. Involved neural structures are not entirely understood. Where and how BT might interfere is not well investigated. Central nervous system effects may exist. BT can also achieve pain reduction by reduction excessive muscle hyperactivity. Additional nociceptive effects may be caused by potentially anti-inflammatory effects.

Pain indications are the latest major extension of BT therapy with chronic migraine being all dominant. As shown in Table 2, altogether 33 LAN publications refer to pain indications.

2.5. Aesthetic Indications

Aesthetic indications are indications where BT is not used to treat a disease, but to improve appearance. All indications presented here are medical procedures reserved for physicians. They are generally not covered by reimbursement systems. Aesthetic indications were developed very early on by neurologists treating blepharospasm. Soon, their potential for aesthetic medicine was realised and strategically developed. Around 50% of global medical BT use is in the field of aesthetic medicine. The contouring of the masseter and the calf muscles is specific to Asian countries.

3. Summary

LAN publications have been produced over a period of more than 20 years, making LAN one of the three longest used BT drugs worldwide. LAN is used for motor, glandular, pain and aesthetic indications. Medical specialties involved are neurology, aesthetics, paediatrics, ophthalmology, urology, gastroenterology, ENT and surgery. Therefore, LAN is used in all major BT indications other BT drugs have been used for. This also documents the widespread use of LAN in China.

Large controlled multicentre studies will eventually become necessary for LAN's registrations in Europe and North America. Further studies on LAN's product details, including its specific biological potency, its production consistency and its stability, will then become necessary. LAN's increased international presence will increase the number of international studies published in international journals.

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