The Important Meaning of LANTOX Intramuscular Injection in Assisting Rehabilitation Training of Children Cerebral Palsy

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Abstract

The new techniques of LANTOX (Botulinum Toxin A) application in corrective therapy of children cerebral palsy dynamic deformity are reviewed. We searched 265 cases of cerebral palsy children who did the treatment, and the total efficacy was 94.6%. In this summary, the method, indications, contraindication, side effects and precautions of the treatment will be explained. The mechanisms of action of LANTOX on remission of spasms, improvement of limb deformity and rebuild of life functions for children cerebral palsy were discussed. For the immune problems of LANTOX, new points of view, new theory and experimental results were quoted, thus further explodes the developmental prospect of this technique. At last, we commented on some contents of the references and represented our opinions and suggestions.

Key words: Children cerebral palsy; Botulinum Toxin A; Dynamic deformity; Corrective therapy; Immunology

The treatment of children Cerebral Palsy (CP) is mainly rehabilitation training. Since the different kinds of secondary deformity resulted by spasm muscle of patient leads to unsatisfactory results in rehabilitation training, the corrective therapy of deformity is very important. The commonly used orthopedic methods are: surgery, manuduction, applications of different kinds of orthopedic instruments and neurolysis, etc. From the beginning of 90s, applications of Botulinum Toxin A (LANTOX) intramuscular injection in remission of muscular spasms were constantly reported, thus the deformities of CP patients were improved, created advantageous conditions for rehabilitation training.

As widely known, LANTOX is a biological toxin with acute hypertoxicity, is the most toxic neurotropic toxin among all bacterial toxins. In clinical treatment, the dosage is limited to ultramicro level, which is equivalent to ng (1/10hmg) level[21], thus will not lead to poisoning of patients and can make the strong hyper toxin a safe and effective drug for curative functions. LANTOX has been applied in ophthalmology clinical since 1980. Literatures of CP combined with LANTOX clinical application were firstly reported by Cosgrove *et al*[5] from Britain on the American Academy of Orthopedic Surgeons 1992 Annual Meeting. In the following year, Koman[15] from American issued thesis

about application of LANTOX in corrective therapy of dynamic deformity, caused value and concern of international scholars. Later on, many reports proved the simplicity, safety and efficacy of the technique. Now it has become a new starting point of science and technical development, but still a new topic. Up till 6th July 1998, there were totally 18 publications about application of LANTOX in CP from US, Britain, Germany, North Ireland, Spanish, South African, Japan, France, Israel and Slovenia upon fetching. In these reported information, the cases varied from 2 to 33, totally 265 cases, total efficacy was 94.6%. The clinical observation and related basic studies were simply summarized as follows.

1. LANTOX Intramuscular Injection and Application Method

Dosage Application: LANTOX is measured in international unit IU. The brand name of US product is BOTOX-A (2.5IU/ng). Generally the clinical treatment dosage is calculated by body weight in kilogram, volume and no. of target muscle, severity of deformity. Koman valued the severity of disease, e.g. for the patients who were incapable of walking and have difficulties in changing postures, the dosage was 2 IU per 1 kg body weight, the highest dosage was 3 – 4 IU per 1 kg body weight; for the patients who had deformity but still capable to walk, the starting dosage was 1 – 2 IU per 1 kg weight. In Sánchez's cases[25], the starting dosage was also 1 – 2 IU per kg of body weight. One week after the first injection, if no effects or effects were unsatisfactory, many will process second injection[1,22,23,26]. Koman[15] clearly stated that dosage should be increased in the second injection, but the highest permitted dosage was 6 IU per kg body weight within 30 days. Although over dosage of LANTOX will not cause clinical symptoms, the cardiac functional parameters indicated that it had certain effects on the autonomic nerve which controls the heart[3].

1 IU of LANTOX is the LD_{50} of intraperitoneal injection of 18 – 20g white rat. Predicted by monkey experiments, LD_{50} of 70kg adult is about 5000 IU[15]. Thus it is safe and reliable for using LANTOX injection at ultramicro level.

Injection Method: LANTOX is in form of water-soluble loose crystals in glass vials. It needed to be stored in fridge of -5 to -20℃. The packages included 50IU/vial, 100IU/vial and 200IU/vial, etc. Diluted by saline according to body weight and need of target muscle. The diluted LANTOX should be used up immediately, or stored temporarily in fridge of 2 – 8℃, but should be used up within 4 hours. According to the muscle size and the depth of the location, needle head with suitable length is chosen, and matched with 1ml syringe. After routine sterilization of skin, the drug is directly injected in target muscle, no local anesthesia is needed. Injection points are

mainly located in the belly of muscle of the nerve muscle joint. 2 – 4 points are injected according to the size and severity of spasm of muscle. It is easier to localize injecting points for the target muscle of superficial layer. It is equivalent to the motor points by electrical stimulus. The target muscle of deep layer is usually overlapped and shielded by surrounding muscles, thus it is impossible to find out the motor points, and in most of the reports EMG detection was used for localization. That is why the operator of LANTOX injection should have anatomy knowledge on nerve muscle and basic knowledge on electrophysiology.

Choosing of Target Muscles: The target muscles should be spasmodic muscles or muscle groups that related to deformity. According to differences of deformity, the common target muscles of upper limbs include: adductor muscle of thumb, deep flexor muscle of fingers, superficial flexor muscle of fingers, biceps muscle of arm, triceps muscle of arm and pronator muscle, etc; for the cross leg, scissors gait and taut foot, adductor muscle group of inner side of thigh and triceps muscle of shank etc are selected respectively. The searching of muscles in deep layer, e.g. popliteal muscle and tibialis posterior, should be especially strict. The 'insulated needle electrode method' proposed by Easton[8] is hard to tolerated by children, it is better to use EMG detection. In conclusion, target muscles should be the main muscles that cause the deformity and dysfunction, if LANTOX injection is inaccurate or wrongly injected into normal muscles, the deformity and dysfunction will be deteriorated.

2. Clinical Efficacy and Side Effect of LANTOX

Evaluation Standard of the Efficacy: The evaluation standards are not consistent. Koman[16] and Sánchez[25] used physician rating scale (PRS), which includes the degree of deformity, rate of walking, test value of angle, parameter of gait, etc. Also adding sit-up, balance upon standing, ability of standing by one leg, etc, the scale standard is 0 – 4 for all those parameters. Zelnik[29] *et al* used CFS that combined with physicians, therapists and parents of patients. Wall[27] *et al* used protractor, hand-dynamometer and dynamic function recording method, etc. Park[20] used X-ray to estimate the degree of changing of talus and calcaneus, evaluated the improvement in deformity. Most of the other efficacy reports are limited to subjective evaluation by eyes for the level of improvement, but no objective quantified strict data.

Efficacy of LANTOX and its Starting Time and Duration: In this summary, we included 18 documentations and there were totally 265 cases of CP, the total efficacy is 94.5%, among them some of the patients processed unexpected results. For example, Garcia[9] presented a case of unstable walking by foot tips which turned quickly into normal

walking after LANTOX injection. Coory[4] *et al* evaluated the improvement in finger function was not ideal. Due to the fact that the function of hand is to finish the finest and most handiness actions, e.g. playing piano, writing, etc, the training of hand has many difficulties, needs long time, and should be processed patiently and adhered steadfastly. Especially because the belly of muscles of hand is smaller, it is hard to guarantee the accuracy of injection.

Most of the authors thought that the starting time and duration of efficacy is 24 hours to 1 week. Firstly, the muscle tension of spasmodic muscle decreases, the deformity is improved, and the functions are obviously increased. Decreases or disappearances of the EMG action potential, decreases in quantum EMG parameter, etc are favorable evidences[2,24] of loosen of muscle. Potential jitter of single fiber EMG expression increases, indicates that the loosen of muscle is caused by transmission disturbance of nerve muscles[17,24].

The clinical durations were not reported consistently. Wall[27] *et al* suggested the average was about 7.6 months. Zelnik[29] suggested the average was 6.7 months. Sánchez[25] concluded after observation of 27 CP cases that the increasing period of LANTOX efficacy after injection was 2 months, the plateau of stable efficacy was 12 – 72 hours, duration of efficacy was 2 – 6 months. He further suggested that duration of hand and foot slowly move type CP was longer than that of spasmodic CP. Watanabe[28] discovered that the efficacy of children CP was better than that of adult CP, and duration was longer, too. In conclusion, starting time of efficacy was within 1 week in most reports. The duration was not less than half year. There were some individual cases processed long term visits for the non-recurrent patients. After LANTOX injection, no matter how long the time is, it is good chance for rehabilitation training and good precautions for prevention of secondary fixed deformity. Also, muscle spasm can lead to ischemic pain, thus it is easy to understand the analgesic action of LANTOX injection on CP[11].

3. Side effect of LANTOX injection

Aching and expanding feeling, painful, temporarily forceless of muscle of injected sites are the commonest side effects[7]. No systematic or general side effects occurs[6]. Herring *et al*[13] suggested conditions of low fever etc were also possible. There are many varieties of starting points, duration and side effects, which may be related to the dosage, operation level, choose of target muscles, severity of disease. What is meaningful is that all reports affirmed that BTA injection is the only easy, safe and effective way of corrective therapy for CP functional deformity, no report about

worsen case has been reported yet. It can sufficiently support people to use this method and encourage people to study the value and prospect of this technique.

4. Indications and Contraindications

Indications: i) Spasm type: functional deformity of CP; ii) Hand and foot slow moving type: CP patients that accompanied with muscle spasm and dysfunction, scoliosis caused by unbalance in paravertebral muscular tone or difficulties in nursing due to limitation of posture changes by pain, etc[10]. iii) Relief of neck muscle spasm, help in completion of cervical vertebral immobilization[22].

Contraindications or Indications with Precautions: i) CP with low muscular tone; ii) Nerve muscle joint transmission disturbance diseases, e.g. myasthenia gravis; iii) Regular deformity of CP patients (should be corrected by surgery); iv) Fever period or during usage of aminoglycoside antibiotic (e.g. gentamycin, kanamycin, neomycin, streptomycin, etc), this kind of drugs enhance toxin side effects of LANTOX, thus one should delay use of LANTOX injection or used carefully under these conditions.

5. Medical Nature and Curative effect of BTA

Medical Nature: In Dec of 1895, 34 members of a club in Belgium ate some corned ham, and then most of them processed clinical symptoms characterized by nerve paralysis. In 1897, Van Ermengem examined botulinum bacteria from the corpses and food of the poisoning event, so the disease was called botulism. Afterwards it was proved that there are 8 types of toxin secreted by botulinum bacteria: A, A, C_1, C_2, D, E, F, G), all are neurotoxins except C_2, which is a kind of cytotoxin. The type A toxin (BTA) is the most toxic among those. It has the best stability, and is easily to be prepared, can be stored in low temperature for a longer period of time. In 1980, Scott[11] firstly used BTA in ophthalmology clinically, then BTA was permitted by FAD as official drug in 1989, and used in CP clinic[5] in 1992.

Curative Effect: The toxin secreted by botulinum bacteria is a double-chain neurotropic toxin, formed by light and heavy chain. The heavy chain is responsible for the binding action, whereas the light chain is responsible for the toxic action[19]. After injection into muscle, BTA processes highly strong compatible effect with pre-synaptic membrane, and seldom has chance to enter blood or pass through brain barrier. This is the main reason for the fact that it does not produce systematic or general clinical side effects. The site of action of BTA is the synaptic structure of nerve muscle joint. After combined with the pre-synaptic membrane, BTA releases release of acetylcholine, phenomenon of losing of nervous control happens at muscle,

leads to reduction of muscular tone and remises muscle spasm. BTA has no destructive effect to pre-synaptic membrane, but only processes muscular loosen effects due to losing of nervous control. The time of muscular loosen is limited to about 3 – 6 months. Afterwards the motor nerve endings will produce new buds and form new motor end plate, restore the original properties of muscle control, thus new spasmodic symptoms occur again. Generally repeated injection is still effective[16].

Immunologic Reaction: There are more and more further reports[18] about mechanism of action of BTA. The serum examination states that BTA can produce antibodies (Ab^+) after entering human body, thus in repeated injection, the BTA is neutralized with BTA antibodies, and loses its original curative effects. If injected with BTB or BTF, the curative effects can be regained[12]. For this, Sankhla[26] mentioned that in some patients, the memonic immunologic reaction of BTA antibodies can be disappeared, then the curative effects can be restored upon repeated injection[30]. On the other hand, BTA antibodies do not affect curative effects of BTB and BTF, this indicates that different kinds of toxin have different immuno specificities, and will not process interacting cross reactions. Directed to the problems of BTA treatment, Hott[14] reported production of an immunotoxin and thought its efficacy is better than that of BTA, the duration is longer.

5. Comment and Suggestion

LANTOX has been applied in CP clinical for only 6 year. Because of its effectiveness and utility, it has been trust and accepted by people, and become the concentration focus of international scholars. LANTOX can loosen spasmodic muscles, but the duration is limited. This limited period of time provided good chance for rehabilitation training, but cannot replace all effects of rehabilitation training. Therefore, LANTOX injection is an important 'assistant treatment' of rehabilitation training.

The production of BTA antibodies severely affects the effects of repeated injection. Use BTB and BTF for injection is still effective, no immuno-cross reaction occurs. According to clinical needs, it is necessary to search and produce other types of toxin products.

The contraction of spasmodic muscles of CP patients make antagonistic muscles stay at extended and pulled condition for a long period of time, thus the antagonistic muscles lose its normal function. Most of the reports valued the treatment of spasmodic muscles, but overlooked the training of antagonistic muscles, this is not good.

Amount of toxin should be measured in international unit (IU). Some authors measured in ng, but did not state the IU value, readers were hard to understand the dosage used, because toxins produced by different countries and factories contain different amount of IU per ng. For the sake of convenience for academic interchange, IU should be used to express dosage.

Since LANTOX is an acute toxic drug, there is high risk if it is used without professional knowledge and familiarity of operation (it usually needs to process under EMG monitoring).

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