Chapter 4
Clinical Use of Botulinum Neurotoxin: Autonomic Conditions

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Abstract Botulinum neurotoxins inhibit the release from cholinergic nerve terminals of the sympathetic and parasympathetic autonomic nervous systems. This has clinical utility in treating conditions involving hyperactivity of the autonomic nervous system, including hyperhidrosis, hypersalivation and conditions of smooth muscle hyperactivity. These clinical uses of the neurotoxin are reviewed in this chapter.

Keywords Botulinum neurotoxin · Autonomic · Hyperhidrosis · Hypersalivation · Sympathetic · Parasympathetic · Detrusor

4.1 Anatomy

The autonomic nervous system, also called the visceral or vegetative nervous system, innervates all inner organs via a dense network of slow conducting nerve fibres. Its function is the—mostly involuntary—maintenance of the equilibrium of body functions under changing environmental conditions. In general, the sympathetic part of the autonomic nervous system adapts the organism to 'fight or flight', whereas the parasympathetic part adapts it to 'rest and digest'. The particular effects of the autonomic nervous system upon the effector organs are shown in Table 4.1.

The autonomic nervous system can be divided into a central part and a peripheral part. Its central part is not well understood. Its main components are the nuclei tractus solitarii, the formatio reticularis and the hypothalamus from where it connects to the hypophysis and other parts of the brain. Its peripheral part consists of afferent fibres called viscerosensory fibres mainly travelling with the sympathetic nerves and entering the spinal cord via the posterior roots. Their cell body is located within the spinal ganglions. Efferent fibres originate from the spinal cord and can be divided into sympathetic and parasympathetic ones. The recent discovery of nitric oxide as a transmitter suggests expanding this concept to include a third efferent pathway. The efferent peripheral autonomic pathways, which transmit virtually all efferences

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Table 4.1 Effects of the autonomic nervous system upon its effector organs

Effector organ	Parasympathetic nervous system	Sympathetic nervous system
Eye	Pupil constriction Accommodation increases	Pupil dilatation Accommodation decreases
Lacrimal glands	Tear production increases	Tear production decreases
Salivary glands	Saliva production increases	Saliva production decreases
Sweat glands		Sweat production increases
Arteries/skin		Constriction Perfusion decreases 'Centralisation' of blood flow
Arteries/intestinal		Constriction Perfusion decreases Blood pressure increases
Arteries/muscular		Perfusion increases
Arteries/kidney		Perfusion decreases
Heart	Heart rate decreases Cardiac output decreases	Heart rate increases Contractility increases Cardiac output increases
Lung	Breathing rate decreases Bronchial constriction	Breathing rate increases Bronchial dilatation
Stomach	Motility increases Acid production increases	Motility decreases
Intestine	Motility increases	Motility decreases
Liver	Glycogenolysis Gluconeogenesis	
Bladder	Detrusor increases Sphincter decreases	Detrusor decreases Sphincter increases
Genitals	Sexual arousal/erection	Orgasm/ejaculation
Adrenal gland		Noradrenaline/epinephrine secretion

except the innervation of striatal muscles, originate from the spinal cord and the brainstem. As shown in Fig. 4.1, the first peripheral autonomic neuron is always cholinergic.

In the sympathetic nervous system, the first peripheral neuron originates from the thoracic and lumbar spinal cord ('thoracolumbar origin'). The second one is located in the paravertebral truncus sympathicus, consisting of its prevertebral ganglia, the ganglion cervicalis superior and the ganglion stellatum and the prevertrebral ganglia consisting of the ganglion coelicaum, the ganglion mesentericum superius and the ganglion mesentericum inferius. The second peripheral neuron is adrenergic and reaches the effector organ. Only the innervation of the sweat glands is cholinergic, thus allowing therapeutic modulation by botulinum toxin (BT). The adrenal medulla is directly innervated by cholinergic first peripheral neurons.

In the parasympathetic nervous system, the first peripheral neuron originates from the brainstem (nucleus Edinger–Westphal, nuclei salivatorii, nucleus dorsalis nervi vagi) or the sacral spinal cord ('craniosacral origin'). The second peripheral neuron is also cholinergic. It is located close to the effector organ. For the pupil, it is located in the ganglion ciliary, for the glandula parotis, in the ganglion oticum and for the glandulae submandibularis and sublinguales, in the ganglion submandibularis. For the heart, lung, stomach, liver, pancreas, kidney and intestine, all innervated by the vagal nerve, and for the rectum, bladder and genitals, the second neuron is located within these organs.

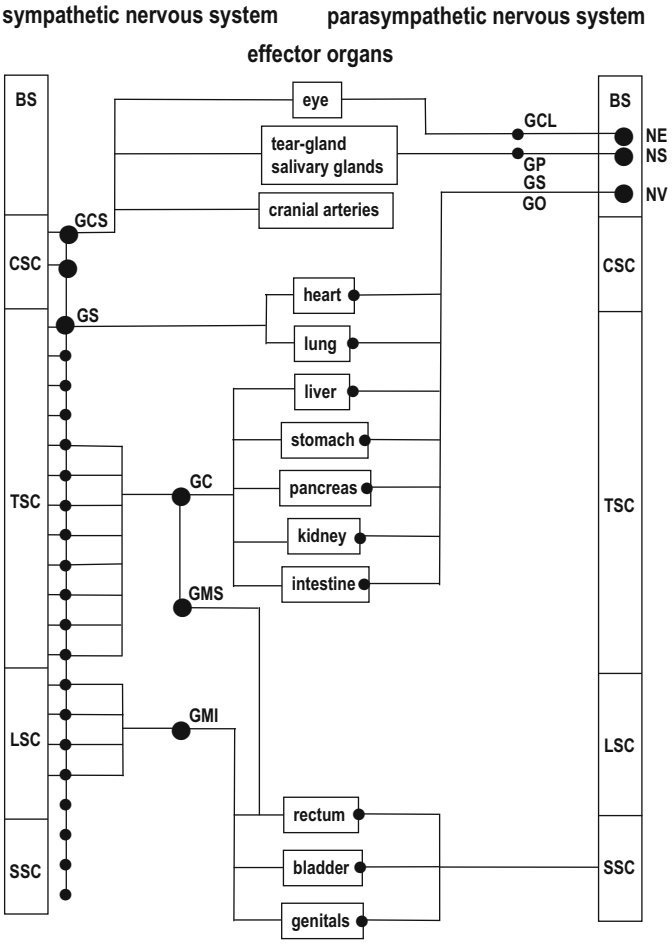

Fig. 4.1 Autonomic nervous system: overview. *BS* brainstem, *CSC* cervical spinal cord, *GC* ganglion coeliacum, *GCL* ganglion ciliary, *GCS* ganglion cervicalis superior, *GMI* ganglion mesentericum inferius, *GMS* ganglion mesentericum superius, *GO* ganglion oticum, *GP* ganglion paroticum, *GS* ganglion stellatum, *LSC* lumbar spinal cord, *NE* Nucleus Edinger–Westphal, *NS* nuclei salivatorii, *NV* nucleus dorsalis nervi vagi, *SSC* sacral spinal cord, *TSC* thoracic spinal cord. (Modified after: Kahle W, Leonhardt H, Platzer W (1979) Taschenatlas der Anatomie für Studium und Praxis. Band 3: Nervensystem und Sinnesorgane. 3 überarbeitete Auflage. Thieme-Verlag, Stuttgart)

4.2 Bladder Dysfunctions (see also Chap. 5)

4.2.1 Anatomy and Physiology of the Lower Urinary Tract

The lower urinary tract consists of the bladder and the urethra. The bladder is emptied by activation of the muscle fibres of the bladder wall, also called M. detrusor vesicae, and by relaxation of the bladder sphincters, i.e. the internal sphincter, formed by

muscle fibres of the bladder wall and supported by the M. puboversicalis, and the external sphincter, formed by muscle fibres of the pelvic floor and supported by the M. sphincter urethrae.

The M. detrusor vesicae, the internal sphincter and the M. sphincter urethrae are controlled by the autonomic nervous system. Its sympathetic part activates the internal sphincter and the M. sphincter urethrae and inhibits the M. detrusor vesicae putting the bladder into 'storage mode'. Its parasympathetic part activates the M. detrusor vesicae and relaxes the internal sphincter and the M. sphincter urethrae putting the bladder into 'micturition mode'. The parasympathetic fibres of the lower urinary tract originate in the sacral spinal cord, their second peripheral neuron in ganglia located close to the bladder. The sympathetic fibres originate in the lumbar spinal cord, their second peripheral neuron in the ganglion mesentericum inferior. The external sphincter consists of striated muscle fibres and is under direct control of the frontal lobe micturition centre via the pyramidal tract and the nucleus Onuf in the sacral spinal cord. The central control of the autonomic innervation of the lower urinary tract is performed by the pontine micturition centre coordinating the sympathetic and parasympathetic efferences.

4.2.2 Detrusor Sphincter Dyssynergia

Detrusor sphincter dyssynergia (DSD) is defined as an incoordinated action of the detrusor and the sphincter muscles of the bladder. It is caused by central nervous system dysfunction and leads to residual urine after micturition causing urinary tract infection, renal damage and urosepsis.

Therapeutic interventions attempt to release the residual urine by catherisation (intermittent or permanent) or reduction of the sphincter tonus by medication or surgery. Problems of these therapies include infections, inadequate efficacy and incontinence. BT therapy for DSD was introduced as early as 1988 by Dennis Dykstra and collaborators [67]. Subsequently, numerous studies [66], [219], [26], [80], [55], [81] confirm robust effects on urethral pressure, post-micturition residual urine volume and bladder pressure for approximately 60–90 days. BT is applied as 100–250 mouse units (MU) Botox® or 150 MU Dysport®. Studies using Neurobloc®/MyoBloc® or Xeomin® have not been published yet. BT injections are performed either transurethrally using cystoscopy or transperineally using electromyography. Other methods for approaching the target muscles include ultrasound [45], magnetic resonance imaging [220] and fluoroscopic techniques [242].

4.2.3 Idiopathic Detrusor Overactivity

Idiopathic detrusor overactivity, also called overactive bladder or urge syndrome, is defined as an urgency to micturate in the absence of pathological processes. Additional symptoms may include incontinence, pollakisuria and nocturia. Prevalence

of idiopathic detrusor overactivity is considerably high and constantly increasing with age. Conventional therapy is based upon anticholinergic drugs. Although effective, this treatment option frequently produces cumbersome systemic anticholinergic adverse effects, especially in the elderly.

BT injections into the detrusor muscle produce robust therapeutic effects on urinary frequency, urgency, incontinence, quality of life and urodynamic parameters lasting for 3–9 months [144], [91], [206], [39], [138], [112], [204], [203], [133], [186]. Two studies are randomised controlled studies [82], [205]. Most studies used Botox®. Use of Dysport® or Myobloc/Neurobloc® was rare. BT doses range from 50 to 300 MU Botox® with most studies applying 200 MU. Dysport® is used in doses of 500 MU. BT is spread over about 30 injection sites. Dilutions are usually 100 MU Botox®/10.0 ml of normal saline. NeuroBloc/MyoBloc®, although used in comparable doses, seems to produce shorter therapeutic effects than BT type A products [106]. When flexible cystoscopy is used for BT application, intravesical local anaesthesia is sufficient. Rigid cystoscopy requires general anaesthesia. Dosing seems critical so that urinary retention requiring clean intermittent catherisation is frequent. Urinary tract infection caused by the procedure is another frequent adverse effect, whereas haematuria is rare [137].

4.2.4 Neurogenic Detrusor Overactivity

Neurogenic detrusor overactivity describes the urgency to micturate usually caused by spinal cord lesions, less frequently by supraspinal lesions. Conventional treatment options are identical to idiopathic detrusor overactivity.

BT therapy is widely published and produces robust therapeutic effects on incontinence, maximum cystomeric capacity, maximum detrusor pressure and quality of life [221], [123], [192], [133], [14], [93], [229], [101], [125], [183], [136], [222], [200], [120], [216], [121], [84]. Two studies are randomised control studies [222], [68]. Target muscle is the detrusor vesicae muscle. The procedure is the same as in idiopathic detrusor overactivity. BT doses vary between 100 and 400 MU Botox® and 500 and 1,000 MU Dysport®. The duration of benefit ranges from 3 to 12 months. Treatment results and adverse effects seem to be similar to those seen in idiopathic detrusor overactivity, only that higher BT doses seem to be necessary [101]. Neurogenic as well as idiopathic bladder overactivity can also be treated in children with Botox® doses of 10–12 MU/kg body weight (up to 360 MU; [119], [107], [216], [195], [215], [214]) or Dysport® doses of 20 MU/kg body weight (up to 400 MU; [3]).

4.2.5 Urinary Retention

Urinary retention may occur in patients with paretic M. detrusor vesicae or overactive urethral sphincters. Causes include cauda equina lesions and peripheral polyneuropathy. BT injections into the external sphincter can improve voiding [182], [132], but also may fail [76].

4.2.6 Bladder Pain Syndrome

Bladder pain syndrome or interstitial cystitis has been treated with BT, with therapeutic effects on pain, daytime micturition, night-time micturition and maximal cystometric capacity [228], [134], [85], [147], [86]. The mechanism of action remains unclear.

4.3 Pelvic Floor Disorders

4.3.1 Pelvic Floor Spasms

Pelvic floor spasms include a number of heterogeneous pain conditions of unknown aetiology which are otherwise difficult to treat. They may respond to some degree to BT. Trials have been reported on vaginism [36], vestibulodynia or coital pain [38], vulvodynia or dyspareunia [96], chronic perineal pain, dysmenorrhoea, dyspareunia, dyschezia, nonmenstrual pelvic pain [1], [111], [240], outlet obstruction constipation [153] and anismus [102], [117], [199]. One study followed a randomised controlled design [1]. Target muscles include the levator ani, obturatorius internus, puborectalis and pubococcygeus muscles. Typical doses per target muscle were in the order of 20–40 MU Botox®.

4.3.2 Anal Fissures

Anal fissures describe painful rhagades of the perianal tissue originally caused by excessive stretching of the anal mucosa and then maintained by inflammation pain-induced increase of the anal tone. Reduction of the anal tone, therefore, offers a therapeutic option. Conventionally, this can be achieved by topical application of isosorbide dinitrate, glyceryl trinitrate, calcium channel blockers or by lateral sphincterectomy. Medical treatment has success rates in the order of 60–80 %. Whilst nitrates frequently produce headaches, calcium channel blockers are better tolerated. Lateral sphincterectomy produces even better therapeutic outcomes and has a low recurrence rate, but bears the risk of permanent incontinence.

An injection of 20–40 MU Botox® or 50–100 MU Dysport® into the M. sphincter ani externus or M. sphincter ani internus can be a therapeutic alternative with success rates between medical and surgical treatment [241], [94], [118], [74]. Often, singular injections may allow the anal rhagades to heal. Subsequent injections may be applied if necessary. Anal fissures may reoccur. Recurrence rates are higher after BT therapy than after lateral sphincterectomy. BT therapy can be accompanied by mild and transient incontinence. BT costs compared to topical medical treatment are a substantial disadvantage. Pros and cons of the available treatment options suggest a stepwise approach starting with calcium antagonists, escalating to BT therapy and eventually initiating surgery [253].

4.4 Prostate Disorders

4.4.1 Benign Prostate Hyperplasia

Benign prostate hyperplasia (BPH), less exactly also called benign prostate hypertrophy, describes proliferation of prostate connective tissue (stromal cells) and epithelial cells in the periurethral prostate (static component) as well as increased prostatic smooth muscle tone (dynamic component). BPH affects a large percentage of the ageing male population and leads to urethral obstruction with urinary retention, pollakisuria, dysuria, urolithiasis and increased risk of urinary tract infection [187]. BPH is believed to be associated with increased local testosterone levels. Conventional therapy includes alpha receptor blockers and anticholinergics for relaxation of intraprostatic smooth muscles as well as 5-alpha-reductase inhibitors to reduce testosterone production. Whilst medication is only partially effective and may produce adverse effects, removal or destruction of periurethral prostate tissue using various minimally invasive or surgical techniques is usually effective, but bears risks of incontinence and retrograde ejaculation.

BT can relax intraprostatic smooth muscles as well as reduce glandular secretion. Animal experiments also suggest induction of glandular apoptosis [56], [48]. Additionally, BT may improve urinary retention by reducing urethral sphincter tone.

BT, transurethrally usually given in doses of 100–200 MU Botox®, can significantly improve flow rate, prostate size and quality of life in BPH patients [154], [135], [46], [47], [48], [226].

4.5 Gastrointestinal Disorders

4.5.1 Gastroparesis

Gastroparesis describes a delayed gastric emptying of non-obstructive origin leading to postprandial nausea, bloating and early satiety. It is caused by dysfunction

of the local autonomic nervous system and may be induced by diabetes mellitus, scleroderma and surgical procedures [258]. In about 30 % of cases, the underlying process is idiopathic [126]. Antiemetics including metoclopramide and domperidone as well as erythromycin may be helpful, but may also be accompanied by adverse effects. Invasive procedures include insertion of jejunostomic feeding tubes, partial gastrectomy and implantation of gastric stimulators.

An injection of 100–200 MU Botox® into the pyloric sphincter can improve cardinal complaints [73], [140], [158], [98], [110], [254], [141], [37], [27], [239], [64], [11], [124], [190], [88]. Two studies followed a randomised controlled design [12], [78].

4.5.2 Sphincter Oddi Spasms

Sphincter Oddi spasms are diagnosed when the sphincteric pressure rises to more than 40 mmHg [251]. They can produce pancreatitis and liver dysfunction. Endoscopic sphincterotomy [251] is the treatment of choice, but bears the risk of perforation and enterocholedochal reflux.

After an initial study performed as early as 1994 [176], several studies showed that 100 MU Botox® can improve the sequelae of sphincter Oddi spasms [249], [251]. Since BT therapy has to be repeated over a prolonged period of time, the use of BT injections as a diagnostic tool to prove the indication of sphincterotomy was suggested [77].

4.6 Oesophageal Disorders

4.6.1 Achalasia

Achalasia describes aperistalsis and reduced relaxation of the lower oesophageal sphincter (LES). Clinically, it manifests with progressive dysphagia to solids and liquids, retention of food and saliva, regurgitation, thoracic pain and weight loss. Its cause is unknown. Inflammation of the myenteric plexus with ganglial cell loss and fibrosis indicates sympathetic degeneration [90].

There is no causal treatment. Symptomatic treatment targets reduction of LES pressure and includes the laparoscopic Heller myotomy and endoscopic pneumatic dilatations. They are successful in approximately 80 % of the cases [197]. Newer approaches include endoscopic myotomy and self-expanding metal stents. The most reliable treatment for achalasia is myotomy followed by dilatation. Both treatments are well tolerated [99]. Pharmacotherapy, including calcium channel blocking agents, isosorbide dinitrate, nitroglycerine, anticholinergics and beta-adrenergic agonists, does not produce satisfactory results [7].

BT was introduced as a treatment for achalasia by Pasricha and his group in 1994 [177]. An injection of 50–200 MU Botox® (usually 80–100 MU) into all four LES quadrants can improve achalasia for 3–9 months [177], [178], [198], [8], [75],

[179], [52], [92], [9], [129], [162], [185], [245], [250], [10], [5], [58], [83], [171], [235], [155], [257], [20]. Adverse effects are mild and transient and include thoracic pain and reflux. Two studies have been performed using 240–250 MU Dysport® for the treatment of achalsia [5], [156]. Results are similar to those using Botox®. BT seems to be reserved for patients who cannot undergo conventional therapies, including elderly patients, patients with comorbidity and patients with oesophageal perforation or epiphrenic diverticula [143]. BT therapy may, however, be combined with conventional therapies for achalasia [259], [15].

4.6.2 Cricopharyngeal Achalasia

In cricopharyngeal achalasia, the upper oesophageal sphincter (UES) is affected, either primary or secondary to various neurological conditions, including stroke and Parkinson's disease, to laryngectomy or to local tumours. UES achalasia can also be treated with myotomy and dilatation. Overall success rates are similar to LES achalasia [95].

UES achalsia can be treated successfully with 10–100 MU Botox® [65], [51], [13], [31], [35], [4], [2], [224], [100], [175], [159], [18] or with 30–120 MU Dysport® [211], [193], [194] applied to the cricopharyngeal muscle. The success rate is similar to myectomy or dilatation and tends to be reduced when complex pharyngo-oesophageal movement disorders are present [95].

4.6.3 Unspecific Oesophageal Spasms

BT injections into the LES have also been used successfully to treat rare forms of unspecific oesophageal spasms [157], [234].

4.7 Hyperhidrosis

4.7.1 Axillary Hyperhidrosis

Hyperhidrosis describes excessive sweating in the axillary region. It is almost entirely idiopathic, often with positive family history, juvenile onset and female preponderance at least in specialised hyperhidrosis clinics. Hyperhidrosis of the palms and soles may be associated. Additional involvement of other typical areas of sweating including the chest, the back or the head is rare. Axillary hyperhidrosis is, with 90 % of cases, by far the most common form of hyperhidrosis. Sweating is physiological and can be separated into thermoregular sweating, predominantly activating eccrine sweat glands, and emotional sweating, predominantly activating apocrine sweat glands. It is difficult to separate hyperhidrosis from normal sweating by abstract or quantitative definition. In clinical practice, however, sweating in hyperhidrotic

patients is usually so strong that reference to quantitative definitions is unnecessary. The frequency of hyperhidrosis is reported to be 2.8 % in the general US population [236]. Hyperhidrosis is medically benign, but may be socially devastating.

Conventional therapies include topical antiperspirants such as aluminium chloride, iontophoresis, anticholinergic drugs and surgery such as retrodermal axillary curettage and endoscopic thoracic sympathectomy (ETS) for palmar and axillary hyperhidrosis. Benzodiazepines, clonidine and non-steroidal anti-inflammatory drugs may have supportive antihydrotic effects. Topical antiperspirants and iontophoresis have short-term effectivity only, and skin irritation may occur. Anticholinergics are usually mildly effective only and frequently produce severe systemic adverse effects. ETS requires a major operation associated with intraoperative risks of bleeding, pneumothorax and haematothorax and post-operative risks of chest pain and compensatory hyperhidrosis elsewhere in the body.

Axillary hyperhidrosis can be effectively treated with multiple intradermal or subdermal injections of BT typically placed about 2 cm apart from each other in the hyperhidrotic skin area. For this, total doses per axilla of 50–100 MU Botox® [40], [166], [104], [167], [149], [150], [61], 100–200 MU Dysport® [212], [213], [207], [105], [160], 2,000–5,000 MU MyoBloc®/Neurobloc® [59], [170] or 100 MU Xeomin® [61] may be used. In almost all patients, hyperhidrosis can be abolished. Adverse effects are virtually nil, except for Neurobloc®/MyoBloc® which may produce autonomic adverse effects [59], [60]. Skin lesions due to dryness of skin do not occur. Injection site pain is unpleasant, but tolerable without further treatment. Due to its disadvantageous pH value, Neurobloc®/MyoBloc® produces increased injection site pain [59]. The duration of the therapeutic effect is often reported to be longer than the 12 weeks typically seen in motor indications. Not surprisingly, a recent formalised assessment of the American Academy of Neurology confirmed that BT therapy is a safe and effective therapy of axillary hyperhidrosis [168].

Future research needs to address the prolonged duration of action of BT for treatment of hyperhidrosis. It should also systematically study dose and dilution optimization for all available products.

4.7.2 Palmar Hyperhidrosis

BT may be successfully used for treatment of palmar hyperhidrosis. For this, 30–160 MU Botox® per palm may be used [169], [163], [243], [201], [181], [231], [225], [148], [227], [256]. Usually, BT doses applied per palm were 50 or 100 MU Botox®, 120–280 MU Dysport® [213], [227], 100 MU Xeomin® [61] or 4,000–5,000 MU Neurobloc®/MyoBloc® [23], [21], [60]. With this, palmar hyperhidrosis can be reduced substantially. Sometimes, for anatomical reasons, hyperhidrotic areas remain.

The major problem of BT treatment of palmar hyperhidrosis is injection pain in the sensitive fingertips. Several approaches have been suggested to reduce this pain,

including cryoanalgesia [230], [22], [196], [145], ulnar and median nerve blocks [41], topical analgesics [30, 180], intravenous regional anaesthesia [33] and iontophoretic BT application [53]. Our experience indicates that ischaemic blockade induced by a proximal arm cuff produces sufficient anaesthesia together with prevention of haemorrhagic BT wash-out. Speedy BT application of less than 45 s per palm also helps improve compliance. Occasionally, mild transient hand paresis may occur. Compensatory sweating elsewhere in the body does not occur.

4.7.3 Plantar Hyperhidrosis

Plantar hyperhidrosis can be safely and effectively treated with 50–100 MU Botox® per planta [165], [244], [223], [42]. Injection pain is a major unsolved problem.

4.7.4 Diffuse Sweating

Diffuse sweating affects the head, the chest and the back. It may also affect, to a lesser degree, the axillae, the palms and the feet. Often, it is symptomatic, caused by infections (viral, bacterial, especially tuberculosis and malaria), endocrine dysfunction (hyperthyroidism, hyperpituitarism, diabetes mellitus, menopause and pregnancy, phaeochromocytoma, carcinoid syndrome, acromegaly), neurological disorders (parkinsonism), malignancies (myeloproliferative syndromes, Hodgkin's disease), collagenosis, drugs (antidepressants, Acyclovir, Ciprofloxacin, etc.), intoxication and withdrawal (alcohol, heroin, cocaine and other substances). Treatment is predominantly causal, if possible. Symptomatic conventional therapy is similar to axillary hyperhidrosis, only more problematic due to its more widespread distribution.

Frontal hyperhidrosis can be treated with 20–90 MU Botox® [127], [208] and cranial hyperhidrosis with around 300 MU Xeomin® [61]. Caution has to be applied to prevent paretic effects upon mimic muscles. Other hyperhidrotic skin areas can also be treated with BT in the same way [[24], Dressler unpublished observations].

4.7.5 Frey's Syndrome

Frey's syndrome, also named gustatory sweating or auriculotemporal syndrome, describes sweating, flushing and erythema of the temporal skin in patients who underwent parotidectomy. After parotidectomy, the parasympathetic nerve fibres originally innervating the parotid gland may aberrantly sprout into the sweat glands and vessels of the temporal skin. Eating, physiologically activating the parotid gland,

then induces sweating and flushing. Depending on the detection method, Frey's syndrome may affect almost all patients with parotidectomy. It is, by far, the most common sequelae of parotidectomy. Although medically benign, it may profoundly affect the patient's social interactions. Conventional treatment includes various surgical interventions, radiation, anticholinergics and topical antiperspirants. It is either of limited efficacy or accompanied by problematic adverse effects.

BT injected into the affected skin produces a safe and reliable relief. Depending upon the affected skin area, 2.5–150 MU Botox® [218], [54], [29], [164], [142], [25], [139], [247], [63], around 2,500 MU Myobloc®/NeurBloc® [43] and 60–80 MU Dysport® [218] may be applied.

4.8 Hypersalivation

Hypersalivation describes the presence of excessive saliva in the mouth which may cause the patient to drool and result in severe embarrassment. Almost always, hypersalivation is caused by impaired swallowing of saliva as in parkinsonian syndromes, in motor neuron disease (amyotrophic lateral sclerosis) and cerebral palsy. Rarely, it may be caused by a genuine hyperproduction of saliva as sometimes seen with the administration of neuroleptic drugs. Conventional therapy includes muscarinic anticholinergic drugs, such as atropine, scopolamine, tricyclic antidepressants for reduction of watery secretion, beta receptor blocking agent for reduction of mucous secretion, radiotherapy or resection of the parotid and submandibular glands, ligation of their glandular ducts, neurectomy of the tympanic nerve, mucolytics and behavioural therapy.

BT therapy of hypersalivation targets the paired parotid glands, producing approximately 30 % of the saliva, and the paired submandibular glands, producing approximately 70 % of the saliva. The paired sublingual glands are difficult to target. With a production of less than 5 % of the saliva, they are not used for BT therapy. BT injections into the parotid gland are easy to place when anatomical landmarks are used. BT placement into the sublingual glands is also easy to perform, although ultrasound guidance has been suggested [114]. The minor salivary glands are spread over the oral cavity and cannot be targeted with BT.

4.8.1 Hypersalivation in Cerebral Palsy

BT has been applied successfully for drooling in children with cerebral palsy, usually under general anaesthesia. Several studies have shown the efficacy of Botox® [113], [71], [237], [115], [116], [209], [16], [191], [252], [6], [173], [210], [232], [255] and Myobloc®/NeuroBloc® [252], [189], [19]. Recommended BT doses depend on the child's body weight. For Botox®, they are 10–50 MU (parotid gland) and 10–50 MU (submandibular gland), for Dysport®, 15–75 MU (parotid gland) and 15–75

MU (submandibular gland) and for Myobloc®/NeuroBloc®, 400–1,000 MU (parotid gland) and 250–1,000 MU (submandibular gland; [188]). Botox® doses of 5–10 MU per parotid seem ineffective [34], [103]. Adverse effects are rare and may consist of dysphagia, weakness of jaw closure, increased saliva viscosity, excessive dryness of mouth and parotitis. Adjunct therapies may include speech therapy, occupational therapy, physiotherapy and behavioural therapy.

4.8.2 Hypersalivation in Parkinsonian Syndromes

BT therapy can be used successfully to reduce hypersalivation in patients with parkinsonian syndromes. For this, a total dose of 10–80 MU Botox® (usually 50–80 MU) is injected into both parotid glands [174], [79], [44], [57]. If additional submandibular injections are performed, the total doses are between 50 and 100 MU with 2/3 of the total dose injected into the parotid gland and 1/3 into the submandibular gland [72], [184]. When Dysport® is used, the total doses injected into both parotid glands are 20–300 MU [28], [89], [146]. When the submandibular glands are to be injected additionally, the total dose is 450 MU [151].

4.8.3 Hypersalivation in Motor Neuron Disease (Amyothrophic Lateral Sclerosis)

BT can be successfully used to treat hypersalivation in motor neuron disease, although disorders of the motor neuron are usually considered contraindications. BT is placed into both parotid glands, sometimes additionally in both submandibular glands. Adverse effects are mild and transient and similar to those seen in patients with parkinsonian syndromes. They included mild chewing difficulties, mild dysphagia and viscous saliva.

For this, Botox® is used in total doses of 12–140 MU with the majority placed in the parotid gland [87], [184], [152], [246]. Usual doses are around 30–40 MU for each parotid gland and around 10 MU for each submandibular gland. Myobloc®/NeuroBloc® is used in total doses of 2,500 MU with 1,000 MU applied to both parotid glands and 2,500 MU to both submandibular glands [109], [49], [50]. Dysport® is used in total doses of 40–150 MU injected into both parotid glands [146].

4.8.4 Hypersalivation Due to Administration of Neuroleptic Drugs

For treatment of hypersalivation induced by the atypical neuroleptic drug clozapine, Myobloc®/NeuroBloc® is injected successfully in both parotid glands in total doses of 2,000 MU and into both submandibular glands in total doses of 500 MU [233].

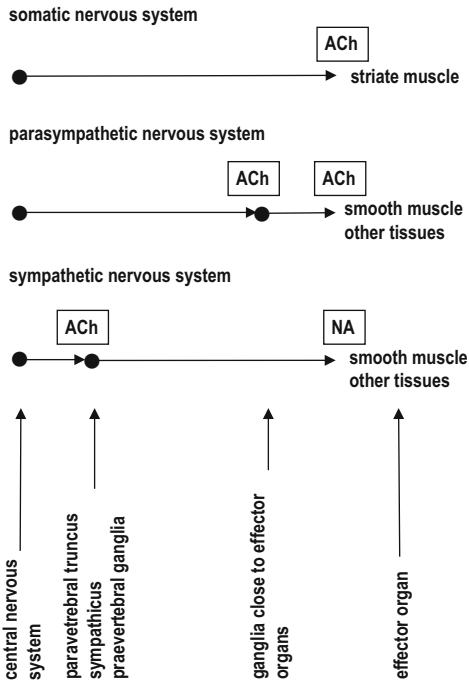

Fig. 4.2 Neurotransmitters in the peripheral somatic and autonomic nervous system. *ACh* acetylcholine, *NA* noradrenalin

4.8.5 Hypersalivation in Various Ear–Nose–Throat Conditions

Occasionally, BT may be used to treat hypersalivation caused by carcinomas of the larynx, pharynx, parotid glands and connective tissues of the neck [69], [70], [202].

4.9 Hyperlacrimation

4.9.1 Crocodile Tears Syndrome

Crocodile tears syndrome describes the uncontrolled flow of tears during eating in patients with facial nerve impairment. It is caused by aberrant sprouting of autonomic facial nerve fibres originally innervating salivary glands. The condition is rare and medically benign. Usually, it is caused by Bell's palsy or traumatic facial palsy; rarely, it maybe congenital. It is named after the observation that crocodiles produce tears when chewing compresses their tear glands [248].

Crocodile tears syndrome can be effectively treated with BT injections directly into the lacrimal gland. For this, 2.5 MU Botox® [108], [17], [128], [248] or 20 MU Dysport® [32], [122], [161] has been used. Occasional ptosis seems to be the only adverse effect. Lacrimal gland injections may also be used for hyperlacrimation after submandibular gland autografts and entropion.

4.10 Other Conditions

4.10.1 Reynaud Phenomenon

BT has been used with controversial results in patients with Raynaud phenomenon [238], [130], [172].

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