Case Series

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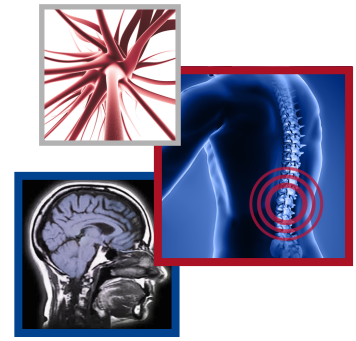
Pain Management



Successful treatment of complex regional pain syndrome with topical ambroxol: a case series

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Practice points

- Complex regional pain syndrome (CRPS) is a complex disorder with poor prognosis without therapy.
- Pathophysiology includes alterations of the autonomic and CNS as well as of the expression of cytokines and neurogenic inflammation.
- Ambroxol is a secretolytic substance but also influences CRPS-related mechanisms.
- It selectively blocks sodium channel subtypes relevant for neuropathic pain, interferes with oxidative stress and inflammation and may influence vasomotor changes.
- Clinical improvements of patients with neuropathic pain symptoms with topical ambroxol cream had been described recently in a case series.
- The present paper describes for the first time positive experiences with topical ambroxol in the patients with CRPS.

Aim: The secretolytic drug ambroxol may be useful for the treatment of neuropathic pain due to its multiple modes of action. We hypothesized that ambroxol may be a treatment option for complex regional pain syndrome (CRPS). **Methods:** Additional to standard therapy, eight CRPS-patients with symptoms of less than 12 months were treated with topical 20% ambroxol cream. Clinical courses were assessed using detailed anamnesis and clinical examination. **Results:** Following treatment we found a reduction of spontaneous pain (6 patients), pain on movement (6 patients), edema (seven patients), allodynia (six patients), hyperalgesia (seven patients), reduction of skin reddening (four patients), improvement of motor dysfunction (six patients) and improvement of skin temperature (four patients). **Conclusion:** Topical treatment with ambroxol cream may ameliorate symptoms of CRPS.

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Keywords: ambroxol • anti-inflammatory action • CRPS • $Na_v1.8$ • neuropathic pain • sodium channel • topical therapy

Complex regional pain syndrome (CRPS) may develop as a complication after limb trauma or surgery and is associated with significant changes in motor, sensory and autonomic systems [1]. CRPS is a debilitating disorder and prognosis is poor without adequate therapy. Pathophysiology of CRPS is the topic of a very lively discussion. Changes in the CNS may explain the complex motor symptoms and also some of the sensory signs [2]. Furthermore, aberrant expression of cytokines and neurogenic inflammation may contribute to the inflammatory signs of CRPS and altered sweating as well as vasomotor changes implies an imbalance within the autonomic nervous system [1].

Therapeutic strategies are multidisciplinary and challenging for physicians. Nonpharmacological treatment includes occupational and physical therapy as well as neurorehabilitation techniques such as mirror therapy and motor imagery. Pharmacotherapy comprises treatment of neuropathic pain, application of anti-inflammatory drugs

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(e.g., glucocorticoids), and agents interacting with bone metabolism (e.g., bisphosphonates). Finally, invasive treatment approaches like spinal cord stimulation should be considered in patients with severe CRPS.

Based on the local and regional distribution of symptoms, local treatment concepts are potentially very important in CRPS. However, so far only few local treatment possibilities have shown a clinical benefit for CRPS (e.g., DMSO cream or topical lidocaine 5% patch and recently a novel compound analgesic cream [3].

Previously, we described the topical treatment of neuropathic pain symptoms with ambroxol cream in a case series [4]. Ambroxol is a secretolytic substance but may also potentially influence several pathophysiological mechanisms involved in CRPS. First, it blocks sodium channels [5]. Therefore, it may ameliorate symptoms of neuropathic pain in CRPS. Second, ambroxol interferes with oxidative stress and inflammation [6]. This may modulate inflammatory signs in CRPS. Third, ambroxol may influence vasomotor changes [7] that are also hallmarks of CRPS. Based on these effects, ambroxol may be an interesting treatment approach for CPRS. However, its use has not been described so far for this disease. In the present paper, we describe for the first time our experience with topical ambroxol in a set of patients with CRPS.

Methods

Eight patients from five centers were treated (generally twice daily) with thinly applied topical ambroxol 20% cream. All treatments were carried out in addition to standard therapy according to guidelines. The patients fulfilled the Budapest criteria for the diagnosis of CRPS. Initially, patients were treated by the investigators during outpatient pain therapeutic sessions, thereafter the patients applied the cream themselves. Treatment durations of 2 days to 4 months were reported, depending on medical history and the course of the disease. The affected area was treated topically with a 20% cream (50.0 g: ambroxol 10.0 g, DMSO 5.0 g, Linola cream ad 50.0 g) [4]. In addition, in three patients measurements of skin temperature were conducted comparing sides, and in three patients the fingertip-to-palm distance was assessed. Pain intensity was assessed using a numerical rating scale (NRS 0-10). All patients gave written informed consent, both for the individual treatment with ambroxol cream as well as for the use of anonymized reports, clinical findings and potential pictures or videos. Documentation and reporting was conducted by each practitioner on the basis of the Declaration of Helsinki as an individual treatment approach.

Results

General effects

Table 1 lists details of the clinical symptoms and response to ambroxol.

Individual case reports

Case report 1

9 months prior to the initial presentation, the 70-year-old female patient developed CRPS type 2 following surgical division of the volar carpal ligament on the right-hand side for the treatment of carpal tunnel syndrome. The entire right hand presented with edematous swelling, glove-shaped allodynia and mechanical hyperalgesia, as well as markedly impaired mobility with a fingertip-to-palm distance of 3 cm. The skin showed red discoloration. Previous medication was 600 mg ibuprofen as required. Topical treatment with ambroxol 20% of the right hand was commenced on 24 June 2016. Pain intensity was reduced 1 h after the treatment from NRS 6 to NRS 5. The fingertip-to-palm distance improved to 2 cm. Pain on closing the fist improved from NRS 8 to NRS 5 (Figure 1). 2 days of consecutive treatment lead to further improvements of spontaneous pain to NRS 4. In addition, the swelling continued to recede.

Case report 2

A 72-year-old female patient presented with CRPS Type 1 which had developed 6 months previously following distal radius fracture on the left hand side. The fracture was followed by 5 weeks of immobilization with a plaster splint. The patient noticed swelling, pain, a blue discoloration and impaired movement of the hand, while it was splinted. When the patient presented with us she reported a pain intensity of NRS 3. She took 500 mg Novalgin/four-times daily and in addition once daily 600 mg ibuprofen; in the previous week, she had also taken 75 mg pregabalin in the evenings. She was receiving occupational therapy and physiotherapy. She presented with an edematous swelling of the entire left hand and impaired mobility with a fingertip-to-palm distance of 0.5 cm. The skin had a livid discoloration. The patient showed increased growth of nails on the hand whereas hair growth on the hand was reduced. Topical treatment of the left hand with ambroxol 20% was initiated on 21 June 2016. For 1

Table 1. Characteristics and outcomes of patients treated with standard treatment plus topical ambroxol 20%.

Parameter	Patient							
	1	2	3	4	5	6	7	8
Age (years)	70	72	34	27	43	53	34	45
CRPS type	2	1	2	2 (recurrence)	1	1	1	1
Cause	Postop.	Fracture	Fracture	Fracture	Postop.	Postop.	Postop.	Fracture
Localization	Right hand	Left hand	Right hand	Right foot	Right hand	Right hand	Right forearm	Left hand
Disease duration prior to treament	9 month	6 month	3 month	1 month (recurrence)	11 month	4 weeks	2 month	3 month
Dynamic allodynia	Yes	No	Yes	Yes	No longer	Yes	Yes	No
Mechanical hyperalgesie	Yes	No	Yes	Yes	No longer	Yes	Yes	Yes
Pain reduction at rest (NRS)	6→5 (after 1 h)	No (3)	7→0-1 (7 days)	7→5 (after 2 h)	Yes	Yes	2-3→0 (few days)	Low baseline pain
Pain reduction during activity (NRS)	8→5 (after 1 h)	No (3)	7-> 2-5	Yes	Attacks-reduction	Yes	6-8→3 (after 1-2 weeks)	Low baseline pain
Pain reduction/follow-up	→4 (Day 2)	no	Yes	Yes (for 3–4 h)	Yes, use 2 month	Yes, use 4 month	Pain-free (Day 21)	Low baseline pain
Edema	Yes	Yes	Yes	Yes	No longer	No	Yes	Yes
Reduction of edema	Yes	No	Yes (after 30 min)	10–20% (after 2 h)	–	–	Yes	Yes
Hyperhidrosis/hypohidrosis	No	No	Yes (hyper)	Yes (hypo)	No	Yes (hypo)	Yes (hyper)	Yes (hyper)
Reddening	Yes	No	(livid)	Yes	No longer	Mild	No	Yes
Improvement of reddening	Yes	–	Yes	Yes (after 3 h)	–	–	–	Yes (after 2 h)
Functional impairment	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Functional improvement	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Skin temperature	Equal both sides	Equal both sides	Alternating	Overheated	Equal both sides	Equal both sides	Overheated (+2°C)	Undercooled
Change of skin temperature	No	No	Normalized	Reduced	–	–	Normalized	Almost normalized

CRPS: Complex regional pain syndrome; NRS: Numerical rating scale.

h following treatment, pain intensity remained constant at NRS 3 and the fingertip-to-palm distance remained at 0.5 cm. Pain while closing the fist remained constant at NRS 3. After 2 days of consecutive treatment, spontaneous pain remained at NRS 3 and the swelling was unchanged. The patient reported a 'comfortably cool feeling' of ambroxol cream on the hand.

Case report 3

As a result of a snow board accident in November 2015, the 34-year-old-female patient had suffered a fracture of the first metacarpal bone and had received osteosynthetic treatment. Since the accident, the patient experienced continuous pain and a swelling which continued after the end of immobilization. In February 2016, CRPS Type 2 with abnormal sensitive nerve conduction velocity of the median nerve was neurologically diagnosed. At initial presentation on 19 February 2016, the right hand was considerably swollen and closing of the fist was reduced to 3 cm fingertip-to-palm distance. In addition, increased growth of hair and sweating as well as allodynia of the scar were present. 5 weeks of physiotherapy had not been beneficial. Treatment with Capsaicin 8% (exclusively on the scar) on 24 February 2016 did also not have any impact on the swelling. Treatment of the back of the hand and the forearm with topical ambroxol 20% on 29 February 2016 lead to a marked reduction of the swelling after only 30 min; finger wrinkles were recognizable again (Figure 2). This was achieved for the first time during the previous 3 months. Initially, the average pain intensity of NRS 7 remained unchanged and after 1 week, the patient

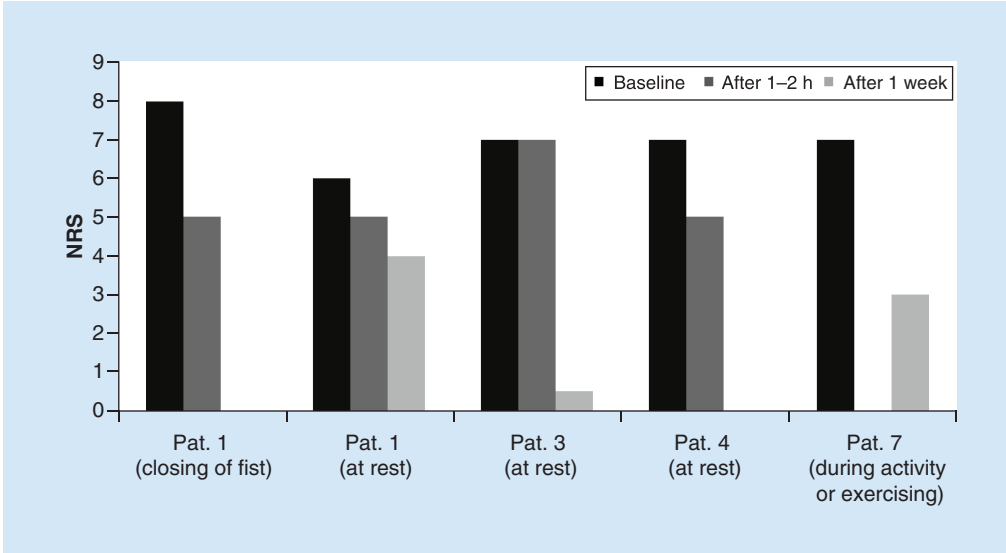

Figure 1. Reduction of pain after 1–2 h and week 1 under treatment with topical ambroxol 20% (single documentation of some patients).
NRS: Numerical analog scale.

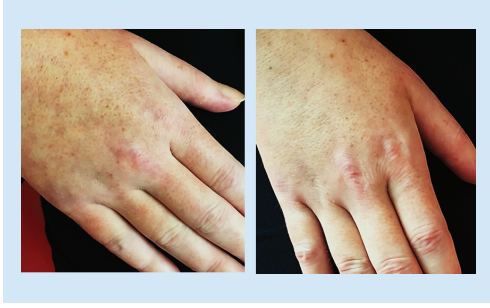

Figure 2. Edema on the back of the hand in female patient three prior to ambroxol 20% cream treatment (left-hand side) and 30 min afterward (right-hand side). Wrinkles of the knuckles are clearly visible again.

reported a pain intensity of NRS 0-1 at rest and NRS 2–5 during movement. For the first few days, she also used 50 mg pregabalin in the evenings. The swelling remained on this reduced level for the first 2 weeks (with once daily treatment during the first week), closing of the fist was easier (fingertip-to-palm distance now 1 cm). The initially seen alternation between marked overheating and coldness of the hand disappeared, after 1 week the hand was consistently 'normally warm' and less livid. The patient did not want to continue use of the cream 'owing to the smell'. Pregabalin had been discontinued owing to ineffectiveness, during the same time period, intravenous regional anesthesia was given twice and alendronic acid treatment once. Mirror box therapy was initiated. The condition of the patient continued to improve under this treatment during the next 2 months. Revaluation after 3 months without ambroxol showed that allodynia, however, persisted but pain, functional impairment and swelling did not reoccur.

Case report 4

Following a tibia fracture of the right foot, the 27-year-old female patient had suffered from CRPS type 1 for several years in the past, and had been successfully treated. Thereafter, she had had few complaints for almost a year, at times even completely free of pain. Approximately 1 month prior to the current renewed presentation of the patient, symptoms of CRPS 'flared' up again. The foot was markedly too warm and showed reddening up to above the ankle (Figure 3). The current episode was triggered by the start of intensive cycle training in conjunction with an increased psychological burden owing to family problems. Any other causes were clinically excluded. Apart from the discoloration, the patient showed dynamic allodynia in conjunction with a complex impairment of mobility. Ambroxol 20% cream led to a reduction in pain from NRS 7 prior to treatment to NRS 5 1–2 h after treatment.

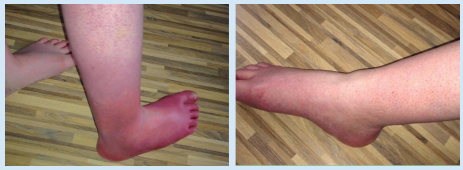

Figure 3. Treatment effect of topical ambroxol 20% in female patient 4:3 h after treatment (right-hand side) swelling of the foot had subjectively receeded by approximatley 10–20% and the area of reddening was reduced to the forefoot.

At the same time, the edema was subjectively reduced by 10–20% and the area of reddening decreased (Figure 3). The swelling reducing effect lasted for 3 h after each treatment. After 6 weeks, the patient was able to cycle again. Ambroxol is still working for meanwhile 7 months, but unfortunately only when regularly used and without a definitive improvement over the time.

Case report 5

11 months after surgery on a ganglion in January 2012, the 43-year-old female patient initially presented in our surgery with CRPS Type 1 which had been diagnosed in another medical surgery. Severe swelling and discoloration, mechanical allodynia and impaired mobility had been present for a long time; pain at movement during the initial presentation was NRS 6-7. Pain was accompanied by persistent hypersensitivity to light touch and pressure, severe sensitivity to cold, and sensation of numbness of the hand. Clinically, however, dynamic allodynia or pin prick hyperalgesia were no longer present. Discoloration and swelling occurred less frequently and closing of the fist was possible again. In addition to neurologic neglect syndrome, referred pain from periscapular, myofascial trigger points into the hand was also present. Initial topical treatment with lidocaine plaster was immediately effective; however, owing to a rash and itching, treatment was switched to ambroxol cream 20%. Again, the patient experienced good efficacy and regularly used this treatment for the successive 2 months. Ambroxol 20% was particularly useful in dampening sudden pain peaks. After 8 months without any medication but with ongoing physiotherapy, the occupational reintegration was successful without reoccurrence of any symptoms.

Case report 6

Four weeks after splitting of the ring ligaments on the third and fourth finger of the right hand, the 53-year-old-female patient was referred from orthopedics with CRPS Type 1. Pain characteristics had changed 2 weeks previously. Deficits in bending and stretching in particular of the third finger and a bending deficit of the fourth finger were found. The skin presented unilaterally dry (without discoloration or temperature changes) and both discrete dynamic allodynia as well as pin-prick hyperalgesia without hypersensitivity to cold were found. Treatment included mirror box therapy, physiotherapy and amitriptyline oral solution for the night and early on in the therapy, both lidocaine plaster and ambroxol 20% cream were alternately used for topical treatment. Topical lidocaine 5% lead to a reduction in pain and the effects of ambroxol 20% cream were described by the patient as being even more pronounced. No other analgesics were used. As soon as 1 week after the initiation of treatment, motor functions had improved considerably; after 1 month, there were only slight impairments of full range mobility. During the four successive months, topical ambroxol 20% in addition to physiotherapy continued to be very beneficial; in particular, at times of more severe pain, it was still used 4 months after the start of the treatment. At this time, additional analgesics had still not been required and the treatment could be terminated. The middle finger still showed impairment of full range stretching but other symptoms kept stable after the end of therapy.

Case report 7

The 34-year-old male patient presented on 15 June 2016 with CRPS Type I on hand and forearm following refixation of a triceps tendon rupture from bone on the elbow. The patient presented with severe motor impairment of the elbow with a stretching deficit of 10–15° and a marked bending deficit. There was mild static and dynamic allodynia of the forearm and severe cold induced hyperalgesia on the wrist. Pain was NRS 2–3 at rest and NRS 6–8 during activity. There was mild edematous swelling of wrist and metacarpus. The skin was cyanotic/pale and showed increased sweating in the elbow. Comparison of the sides showed a 2°C increase in temperature on the right-hand side (measurements 3× per week on the dorsal forearm/wrist). Apart from increased growth of hair on the volar forearm, there was reduced growth of nails. Ambroxol 20% treatment was conducted 3× daily on

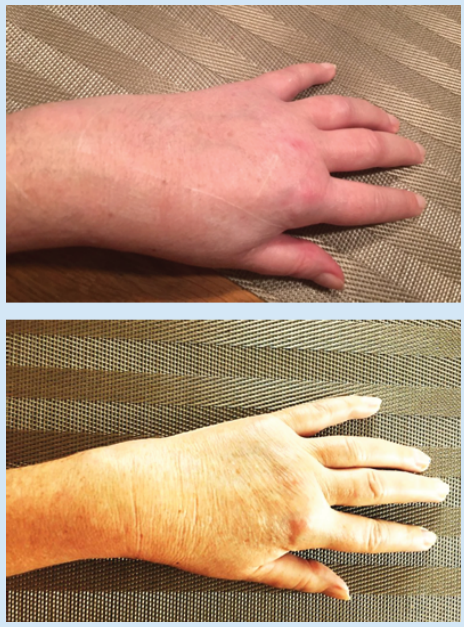

Figure 4. Edema on the dorsum of the hand in female patient eight prior to ambroxol 20% cream treatment (above) and 150 min afterward (below). Comparable with patient three (Figure 2) swelling is reduced and wrinkles of the knuckles are clearly visible again.

the right forearm and wrist, each time followed by a slight tingling sensation. In parallel, the patient underwent daily occupational therapy and an inpatient multimodal therapy program with a single stellate block. After 5 days only, he reported a marked reduction in pain up to being completely pain free. Active mobilization was possible early on. Exercises under ambroxol 20% treatment were accompanied by considerably less pain that without prior treatment. Furthermore, the edematous swelling was reduced within 14 days, and skin condition and temperature were equal on both sides at this timepoint. The patient was discharged on 8 July 2016 without ongoing ambroxol therapy; he was free of pain and showed marked improvements concerning the range of mobility of wrist, elbow and shoulder joints.

Case report 8

3 months before the first visit, the 45-year-old female patient developed CRPS Type 1 following distal radius fracture on the left-hand side. The entire left hand was hypothermic and presented with edematous swelling, patchy mechanical hyperalgesia, but without dynamic mechanical allodynia. Function was markedly impaired with a fingertip-to-palm distance of 3 cm, an inability to reach any finger with the thumb and a complex reduced mobility of wrist. She showed increased growth of nails and hairs combined with a discrete hyperhidrosis. Interestingly except for the initial phase after the fracture, she reported a surprising low pain level all over the time. Topical treatment with ambroxol 20% was commenced three-times daily combined with occupational therapy and topical lidocaine over the night-time. Ambroxol 20% alone was able to significantly reduce edematous swelling within 2.5 h (Figure 4). 17-days later swelling remained reduced as well as hyperhidrosis and sensation of cold. All fingers except finger 5 could be reached by the thumb and also subjective mobility of the wrist was improved.

Discussion

This case series describes for the first time CRPS patients with symptoms of less than 12 months who experienced pain relief and functional improvements following topical ambroxol. This can be explained by a sodium channel blockade and antioxidative, anti-inflammatory and vasomotor properties. We summarize putative modes of action in Table 2.

Sodium channel blockade, analgesic effects

Ambroxol is a secretolytic agent blocking sodium channels similar to the well-known local anesthetics [5] but 40-fold more potent than lidocaine [8]. None of the compounds used for neuropathic pain to date shows a comparable selectivity for the blockade of the nociceptor specific TTX-r-channel subtype $Na_v1.8$, which appears to play a role

Table 2. Potential pathophysiological and clinical associations between complex regional pain syndrome and action of ambroxol (according to literature).

Mechanism	CRPS	Ambroxol
Inflammation		
Inflammation	Present	Anti-inflammatory
Edema	Present	↓
Cortisone	Helpful	Comparable efficacy
Tissue hypoxia and acidosis	Present	↓
Cytokines		
Proinflammatory:		
– IL-1	↑	↓
– IL-2	↑	↓
– IL-6	↑	↓
– IL-12	↑	↓/↑ ?
– IFN-y	↑	↓
– TNF-α	↑	↓
Anti-inflammatory:		
– IL-4	↑/↓ ?	↓
– IL-10	↓/↓ ?	'Stabilization'
Others:		
– IL-8	↑/↓ ?	↓
– IL-13	↑ (Trend)	↓
– Leukotrienes (cys-LTC-4)	↑ (Involved?)	↓
– Mast cells	↑ (Involved)	↓ (Secretions)
Oxidative stress		
Oxidatative metabolites	↑ (Key function)	↓
Free radical scavenger	Effective	Acts as
Lipid peroxidation	Antagonists beneficial	Inhibits
NO	↑ (Via IFN-y)	Activity/production ↓
Adrenergic/vascular system:		
– Adrenergic receptors	Expression + sensitivity ↑ Stimulation ≥ IL-6 ↑ Associated with $Na_v1.8$	IL-6 ↓ $Na_v1.8$ blockade
– Vasoconstriction	↓	↑
– Vascular permeability	↑	↓
– Acetylcholine receptor	Involved as agonist?	Reduces Ach-effects
– Noradrenaline	↓	↑Concerning efficacy
Nociception/nervous system:		
– Central sensitization	↑	↓ ($Na_v1.8$ blockade, inflammation ↓)
– Neuropathic pain	Present	↓
– Allodynia/hyperalgesia	↑	↓
– Neurodegeneration	Involved?	↓
– NK1 receptor	Expression ↑, increases $Na_v1.8$	$Na_v1.8$ blockade
– Sodium channels	Expression ↑	Na-channel blockade
– Topical lidocaine	Effective	40-fold more potent
– $Na_v1.8$ sodium channel subtype	On sympathetic nerves basis for calcitonin effect? ↑ on Aβ-fibres blockade via alpha-2 agonists expression in causalgia pain involved in CRPS pain?	$Na_v1.8$ blockade

CRPS: Complex regional pain syndrome; NO: Nitrogen monoxide.

in CRPS [9], nociceptor sensitization and maintenance of neuropathic pain [10]. $Na_v1.8$ seems important for cold pain [11] and can be expressed by sympathetic neurons [12]. Particular importantance for our observations is that an experimental blockade was most effective locally (vs intrathecally (i.th.) and systemically) [13].

Na_v 1.8 expression, allodynia

$Na_v1.8$ is selectively expressed by nociceptive, sensory neurons and neurons of the dorsal horn, is overexpressed in neuropathic pain and involved in spontaneous neuronal activity [14–16]. $Na_v1.8$ is transported to peripheral areas during inflammation and massively increased in myelinized axons, facilitating peripheral sensitization and hyperalgesia (as in CRPS) [17]. A blockade (e.g., through ambroxol) reduces mechanical, thermal and visceral hyperexcitability [16]. Frequently co-expressed with $Na_v1.8$, also $Na_v1.7$ is found in peripheral sympathetic neurons, involved in inflammatory pain and blocked by Ambroxol [18]. A functional upregulation of $Na_v1.8$ also in afferent A-β-fibres in chronic peripheral inflammation emphasizes its participation in mechanical allodynia and persistent inflammation [16]. Thus, an increased channel expression in skin biopsies of painful skin in CRPS [9] is not surprising.

Six of our patients suffered from mechanical hypersensitivity, a condition already found to be improved by topical ambroxol [4,19]. Ambroxol mostly suppressed heat and cold hyperalgesia and mechanical allodynia [15,16]. As ambroxol also reduces inflammation-induced mechanical allodynia and monoarthritis pain [15], its antiallodynic effect is not necessarily restricted to neuropathic pain. Finally, TNF-α, increased in CRPS skin biopsies and likely involved in hyperalgesia [20], is decreased by ambroxol [6,21].

Inflammation, edema and reddening

Inflammatory processes in CRPS (rather localized that systemic) are unopposed. We recently found reductions of nociceptive pain following topical ambroxol [19] as before described in animal experiments [15]. The significance of proinflammatory cytokines in CRPS is undisputed and ambroxol inhibits these manifold (Table 2) [6]. Therefore, CRPS patients should benefit from ambroxol and reduction of edema in five of our patients but also an improvement of reddening in four of them confirms this (Table 1). In biologically relevant dosages, ambroxol can increase vascular contractions [7] and it improves vascular permeability with a potency comparable with dexamethasone [21]. Further $Na_v1.8$ blockade occurs quickly and affects vascular and inflammatory processes.

Oxidative stress

Oxidative stress plays a key role in the development of CRPS and antioxidants are used for the treatment [22]. Nitrogen monoxide is increasingly released from monocytes in CRPS following IFN-γ-provocation [23]. Ambroxol counteracts this; it reduces IFN-γ and nitrogen monoxide [6]. A reduction of many other oxidative metabolites by ambroxol also is ensured [24]: it not only prevents oxidative stress, but also exhibits a scavenging action concerning already present radicals. Oxygen radicals have a key function in ischaemia-induced neurodegeneration as in CRPS. Ambroxol, however, lowers ischaemia-induced nerve damage [25], protects tissue from cold damage [26] and heat-induced lipid peroxidation [27].

Autonomic nervous system & neurodegeneration

$Na_v1.8$ receptors in fascicles and cardiac myocytes, are often closely associated with small capillaries [28]. They were also found in the sympathetic superior cervical ganglion [12]. A sympathetic failure as part of the disease is undisputed, for example, as an impaired sympathetic vasoconstrictor reflex [29]. Ambroxol induces or increases vascular contractions following adrenergic stimuli [7]. This appears to be one more pathway through which topical ambroxol may also exert an effect. Furthermore an association between CRPS neuralgia and distal small fiber neuropathy, in which increased $Na_v1.8$ expression occurs, is discussed.

Functional improvements

Functional improvements were seen in six of seven patients. Four of the affected patients reported this as early as 30 min to 2.5 h and the others within 1 week (Table 1). Initially, this could be interpreted as a result of pain reduction, however, cases 3, 4 and 8 also showed a reduction of edema after a very short time (Figures 2, 3 & 4). For neuropathic foot pain and finger polyarthrosis, we earlier also observed marked functional improvements after such a short time [4,19].

Onset, duration, safety & dosage

$Na_v1.8$ blockades by ambroxol start *in vitro* within a few seconds [5]. Hypersensitivity in rats was reduced after approximately 30 min for 3 h [30]. This corresponds well to analgesic effects in some of our patients beginning as soon as 1–2 h (Figure 1 & Table 1). In other observations for neuropathic or nociceptive pain, the topical ambroxol effect started after 5–30 min, lasting 4–8 h [19]. None of our patients reported adverse drug or skin reactions. Even IV administration of 1 g is approved and well tolerated and there are reports of up to 3g/d IV over 53 d [15].

Conclusion

The secretolytic agent ambroxol exerts a strong local anesthetic effect, has pronounced antioxidative and anti-inflammatory properties and an impact on vasomotor function. In the current study, treatment with topical ambroxol 20% cream has for the first time successfully been put into practice in CRPS patients. As they all had symptoms of less than 12 months the results cannot necessarily be extrapolated to cases of long-lasting CRPS where central cortical or glial changes are thought to predominate. Furthermore as multiple treatments were co-applied it is difficult to isolate out the exact effects of ambroxol. However, these preliminary results suggest that further research in this area is warranted.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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• **As in CRPS at least in later stages of the disease appear central nervous changes. This is important to realize as this fact may limit a potential ambroxol response.**

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