Review Article

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The Procaine-Base-Infusion: a Review after twenty Years of Use

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ABSTRACT

The highly-dosed infusion with Procaine-HCl with sodium-bicarbonate as additive was firstly published twenty years ago. The method advanced to a routine in many centers for pain treatment, rehabilitation and natural medicine. The aim of the procedure is the systemic use of the various pharmacological features of Procaine, especially to inhibit pain and inflammation, for vasodilatation, anti-oxidation and to harmonize the vegetative nervous system. On one hand shall the addition of sodium-bicarbonate balance the common latent pH-decrease in the periphery. On the other hand also the degradation products of Procaine (DAE and PABA) have a systemic effect. For the safety of the patients and to improve the success rate of the method it was shown that the classic Procaine-Base-infusion should be only realized on the base of a prior acid-base-diagnostic.

Keywords

Inflammation, Infusion, Procaine, Pain, Rheumatism, Sodium bicarbonate.

Procaine - The "Polycrest" of Anesthetics

The local anesthetic Procaine is characterized by a sum of pharmaceutical features. With this in mind Prof. ASLAN, the founder of the eponymous therapy, spoke of it as vitamin-like action beside the anesthetic effects [1]. Further benefits of Procaine are its good tractability and low-grade toxicity due to its short half-life and plasma degradation, the capillary impermeability effect [1], the inhibition of inflammation [2-5], antioxidative and fat-reducing action [6-8]. Contrary to all other anesthetic drugs it causes vasodilatation of vessels and capillaries [9-14]. Therefore, with this therapy it is possible to reach and optimally influence very poorly circulated tissue (especially in case of inflammation and pain). Beside the effect of blocking voltage-dependent sodium channels with the result of a short-term anesthesia [15], additional actions of Procaine on cell membranes and the matrix as well as sympatholytic actions were also discussed [16-21]. KRAUSE has demonstrated that the anti-inflammatory effect of Procaine in rheumatic disease was especially high when combined with an alkali additive [7]. In the field of oncology, the effect of Procaine to reduce side effects from radiotherapy [22,23] or to improve the influence of chemotherapy [24-27] is reported. Furthermore, a wide epigenetic action of the procaine has been demonstrated. A growth-inhibition after incubation with human cancer cells due to the partial blockade of DNA-methylase in vitro was described in 2003 [28]. A diminishing effect of the proportion of 5-methylcytosine into global genomic DNA and cell proliferation due to procaine was reported in a study of tumour suppressor genes [29]. In the same way, inhibition of DNA methylation in human hepatoma cells was found by TADA et al. [30]. In 2016, SABIT et al., showing that the use of procaine combined with carboplatin was the most effective treatment for diminishing the global level of DNA methylation in colon cancer cells [31]. Well examined is also the central modulation of Procaine acting on the stress axis of limbic system with anti-depressive and psycho-analeptic action [32-36].

The Procaine-Infusion – the logic following of other parenteral applications

Depending from the amount of administered Procaine it is possible to increase the effect to influence pain, inflammation and to reach the other described features of the substance (Figure 1). Since a long time it is prevalent to finish a neural therapy session with an i.m. or i.v. shot of 25 till 50 mg Procaine to reach a systemic action. The pure Procaine infusion was firstly described by SEIFEN et al. [37,38] and was mostly used as a continuous treatment in cases of acute pancreatitis [39-41] and for epidural anesthesia in infants,

children and risk patients, which underlines the low toxicity of the substance [42-49]. O´DONNELL et al. reported about the use of procaine infusion to block the cardiac nerves [50].

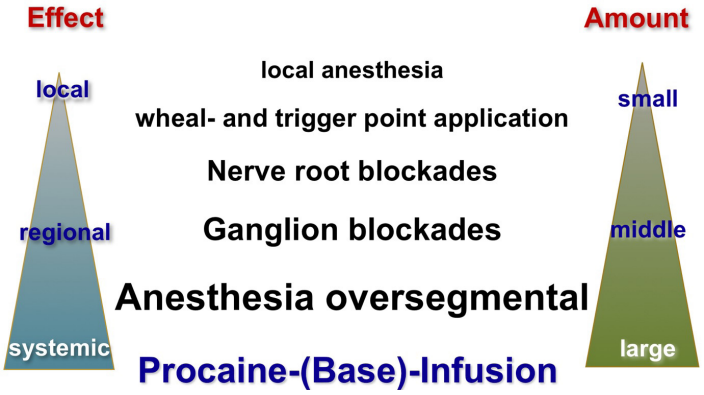

Figure 1: Fields of parenteral Procaine applications.

Presently it is reported that long-term relaxing, anti-depressive and anxiolytic effects are often observed when IV applications or short term infusions of Procaine are given [51,52]. It has been demonstrated that when procaine is administrated intravenously in humans, it increases blood flow of anterior para-limbic zones and the amygdala cerebral [53] as well as to improve hemodynamic effects of the heart [54]. Other areas of limbic system have been studied when procaine is administered in animal models, finding action on many muscarinic cholinergic receptors of hippocampus. Several authors have been reported procaine actions on many biochemical systems such as dopamine, norepinephrine, serotonin, glutamate, among others. For these reasons, procaine is considered as useful for studying limbic system and emotions [55,56].

In a recent research, it has been pointed out that procaine injection into the ventral tegmental area is able to suppress temporarily the fear conditioned avoidance response in rats and also acts on hippocampal theta rhythms which are related with arousal and attention [57]. Apparently, the metabolites of Procaine are responsible for the additional pharmacologic actions. DEAE is able to act as an anti-inflammatory due to the inhibition of the fatty acid amide hydrolase which causes an increase in endocannabinoid levels [58,59]. The second metabolite PABA operates as an antihistamine, capillary sealant and as a stabilizer for the membranes due to the ester binding with ceramide [60-62].

The increase of infusion effect by combination with sodium-bicarbonate

With the aim of combining the well-known pure alkaline infusion [63] and the pluripotent features of Procaine, the first study was published as the so-called “neural infusion therapy” in 1997 [64]. After impressive positive results were demonstrated in chronic pain patients [65], the method gained popularity very fast in the German-speaking countries and was incorporated into textbooks of pain and neural therapy [66,67]. GLUSA et al. were also able to confirm the vasodilatation effect of the Procaine-Basemixture by using an animal model [68]. An increase of intra-cellular Procaine concentration due to the addition of sodium bicarbonate [69] and an accelerated initial effect were also observed in animal studies [70,71]. The continuous application of Procaine-Base by the use of a medical pump demonstrated impressive results in many severe cases of pain and inflammation [72-74].

With the osteoarthritic model of rats the anti-rheumatic and joint-protective action of Procaine-Base after intra-articular injection was clearly superior compared to giving the drug Dexamethason [75].

The primary aim of additionally adding the natural buffer-base sodium bicarbonate was its plasmatic degradation influence on Procaine due to the action of serum esterase. All local anesthetics have the common characteristic of general build-up and ionization. These characteristics are essential for their action on the voltage-dependent sodium channels. The unloaded Procaine molecule represents the transporting structure which is able to permeate. The loaded form, Procaine-H+ (ionized form) binds the sodium channel receptor and thus blocks the propagation of an impulse. By changing the pH value of the solution and the terrain, the ionized and non-ionized forms of Procaine can be influenced [76]. It is known that different sodium bicarbonate concentrations can influence the intracellular pH [77].

Initially it was postulated that under more alkaline conditions the conversion of Procaine to para-amino-benzoic acid (PABA) and diethyl-amino-ethanol (DEAE) will be distinctly reduced. Contrary to this assumption it is believed that after intravenously injecting Procaine-Base it gets diluted in the blood of big vessels leading to a quick drop in pH reaching normal physiological levels. In addition, the pulmonary circulation will cause a respiratory compensation of alkalosis. The actual retardation of Procaine degradation can be explained as follows: The pH-dependent dissociation shift explained above will result in increased amounts of well-penetrating transport forms. This is generally typical for all local anesthetics and thus 3-40% of the liberated base is present depending on the pKa value of the anesthetic drug. Besides the distribution in a steady state, the speed of distribution is also important. The speed of distribution is the limiting factor meaning that the diffusion through the membrane is the speed determining step [78]. Accordingly, the distribution depends directly on the lipophilicity of the agent. By shifting the pH, the lipophilic features are changed. A higher amount of free base implies also a higher amount for permeation, which is immediately available to the surrounding tissue and cannot be metabolized so easily by the serum esterase [40].

Practical application of Procaine-Base-Infusions

If there is no prior information concerning the tolerance of Procaine before the infusion, we recommend to make a test application of one drop Procaine 1% into the conjunctiva. Normally, immediately redness (due to increased blood flow) can be observed, a numbness sensation and perhaps a quick burning sensation (due to HCl) can be reported by the patient. If the burning pain persists for some minutes please abstain from parenteral infusions. It is important to highlight that only Procaine-HCl with a pharmaceutical permission

for IV application and without any preservatives (e.g. parabens) should be used.

We recommend to start with a dosage of 50-100 mg Procaine-HCl and 20 ml sodium hydrogen carbonate (8.4%) diluted in a 250 to 500 ml carrier solution. Meanwhile the isotonic sodium chloride solution, used routinely for many years can be exchanged by a similar electrolyte solution to prevent hypernatremia. The infusion takes place for approximately 45 – 60 minutes. By adding increments of 50 mg Procaine-HCl and 10 ml sodium bicarbonate (8.4%), the Procaine-Base infusion will be titrated until the desired therapeutic effect has been reached. For a normal-weight person the maximal dosage of Procaine-HCl is 300 mg (see dosage Table 1). In patients with cardiovascular risk factors we recommend the use of a surveillance technique (EKG, oximetry) for dosages above 300 mg Procaine-HCl. It is advised to ensure an after-treatment observation period of 30 minutes. Furthermore, it is advised to avoid driving for about one hour after treatment. Because of the stability of the Procaine-Base-mixture it should be used up within two hours [because of progressing degradation of Procaine]. Without any prior acid-base diagnostic the Procaine-Base infusion should not be administered more than three times per week with a minimum of one day break between treatment days. A series of 6 to 10 infusions depending on the medical condition have been approved.

Procaine dosage 1 %	sodiumhydrogencarbonate dosage 8.4 %	Sodium chloride 0.9 %	Total volume
100 mg = 10 ml	20 ml	500 ml	530 ml
200 mg = 20 ml	40 ml	500 ml	560 ml
300 mg = 30 ml	60 ml	500 ml	590 ml
400 mg = 40 ml	80 ml	500 ml	620 ml
500 mg = 50 ml	100 ml	500 ml	650 ml

Table 1a: Table of dosage in case of using Procaine 1%.

Procaine dosage 2 %	sodiumhydrogencarbonate dosage 8.4 %	Sodium chloride 0.9 %	Total volume
100 mg = 5 ml	20 ml	500 ml	525 ml
200 mg = 10 ml	40 ml	500 ml	550 ml
300 mg = 15 ml	60 ml	500 ml	575 ml
400 mg = 20 ml	80 ml	500 ml	600 ml
500 mg = 25 ml	100 ml	500 ml	625 ml

Table 1b: Table of dosage in case of using Procaine 2%.

The classic blood parameters for inflammation like blood sedimentation rate and Creactive protein (CRP) should improve after a series of Procaine-Base infusions. Almost always after four till six applications the patients report much better mood and improved overall condition. If there is a positive reaction to the treatment (so-called "responders", in approx. 80 % of patients) it is advised especially in chronic diseases, to continue with a long-term therapy using the helpful dosage for longer intervals, e.g. one till twice a month [34-36].

How safe is the Procaine-Base-Infusion and which side effects appear?

The hypersensitivity to Procaine (also called "para-group allergy") reported in old textbooks with an increased allergy rate has not been confirmed yet [79,80].

After over 450.000 applications of neural therapy infusions according to the described regime in our clinic and outpatient department, we have not observed one case with long-term or severe side effects. No case was registered with a serious allergic emergency situation, which underlines the observations of BECKE concerning the huge therapeutic safety of Procaine [58]. Sometimes patients report of heart palpitation (6%) and profuse sweating (5%). According to our experience patients which are using nitro compounds, calcium antagonists and beta-blockers seem to have a higher disposition to these side effects. Apparently in such cases the reflective and oversegmental disinhibiting effect of the anesthesia dominates over the negative-ionotropic and negative-rhythmotropic potential of Procaine. As expected, in approximately 6% of patients a short-time reduction in blood-pressure and vasovagal syncope situations can occur during the application. All these symptoms disappear within few minutes, especially after reducing the infusion speed [34,63].

Some patients report about sleep disorders (5%) and a general hyperactive feeling till one day after finishing the infusion, which does not reduce the physical working capacity. Approximately 4,5% of treated persons complained of temporary headaches and slight vertigo. Especially during the first couple of infusions such reactions can occur in scope of a so-called "first reaction" (HERING´s effect) according to the holistic thinking in neural therapy [1] and homeopathy [81].

Indications and contraindications of Procaine-Base-Infusions

The multiple therapeutic effects of Procaine in combination with an alkaline additive are responsible for the enormous palette of medical indications (tab. 3a). Especially all kind of pain, inflammatory and auto-immune diseases, vegetative imbalances in addition to the complementary cancer treatments are of primary importance.

Acute situations	Radicular syndrome, pseudo-radicular syndrome, acute infection, early stage of algodystrophy, sudden deafness, inflammations, Migraine, activated osteoarthrosis, postoperative pain treatment
Chronic pain	Multiple arthralgia, chronic radicular-/pseudo-radicular syndrome, Algodystrophy, all kinds of neuralgia, facet pain syndrome
Chronic inflammations	Lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, scleroderma, neurodermatitis, multiple sclerosis, crohn´s disease, ulcerative colitis, polymyalgia rheumatica
Others	Periphery circulatory disorders, constipation, dysmenorrhea clinical and para-clinical hints for tissue acidosis, osteoporosis complementary cancer therapy, pre- and post-operative

Table 3a: Main indications of Procaine-Base-Therapy.

The few contra-indications should receive attention in practice

which are summarized in table 3b.

Patient	Hypersensitivity towards Procaine, Neurosis or Psychosis with unclear compliance See also expert information at Procaine and Na-bicarbonate producers
Therapist and Staff	Lack of knowledge in handling local anesthetics, inadequate educated staff, Under-resourced rooms and lack of adequate emergency equipment

Table 3b: Contra-indications of Procaine-Base therapy.

Current status: Procaine-Base-Infusion adapted to the acid-base-balance

It is important to emphasize that according to the above described procedure of Procaine-Base-infusion, a daily application of such a high dose of sodium bicarbonate is inacceptable. SAHA reported that after a total of seven Procaine-Base-infusions with daily increasing dosages up to a maximum of 300 mg Procaine-HCl and 120 ml 8,4% sodium bicarbonate, 3 out of 13 patients showed clinical symptoms of metabolic alkalosis [82]. Before and after these series of infusions the base excess (BE) measured via arterial blood gas analysis was determined and in all cases amounted to over plus two, which indicates a verified metabolic alkalosis. This kind of daily treatment only applies for patients with an adequate acid-base homeostasis. The body intrinsic buffer system should not be overloaded.

However, patients having a metabolic alkalosis with a reduced compensatory ability in acid-base balance are increasing. Quite often this is found in cases of verproteinization, advanced stages of cancer, liver weakness and putrefaction dysbiosis of the large intestine. Furthermore, the use of antacids, alkaline powders, loop diuretics and too much sodium intake enhances the shift in the acid-base-balance towards alkalosis [83,84]. For the practical analysis of the acid-base balance we prefer the venous blood titration system BUFFY® over the arterial blood gas analysis (aBGA, see [85-88]) because it is hematocrit-adapted and calibrated to 37°Celsius. The test gives very good information about the buffer capacity of whole blood and plasma and indicates exactly the amount of base needed [88,89]. Metabolic alkalosis can also occur in hyponatremia, hypokalemia and in increased ammonia levels (in EDTA plasma). In cases of inflammatory, cardiac and renal dysfunctions, rheumatic and pain-related diseases a metabolic acidosis is mostly likely detected [91]. These patients have an increased need of a buffer base and should receive sodium bicarbonate ranging from 60-120 ml (8,4% solution) in addition to Procaine.

In contrast to cases of metabolic alkalosis there is only a small or no need of additional base treatment. In this case, we only administer infusions of Procaine-HCl together with a carrier solution. In addition we suggest to give 3-5 ampules of L(+)-lactic acid.

In figure 2 the pH-values of different concentrations of Procaine-HCl, different alkaline mixtures and basic solution volume as well as the pure Procaine-HCl solution are compared.

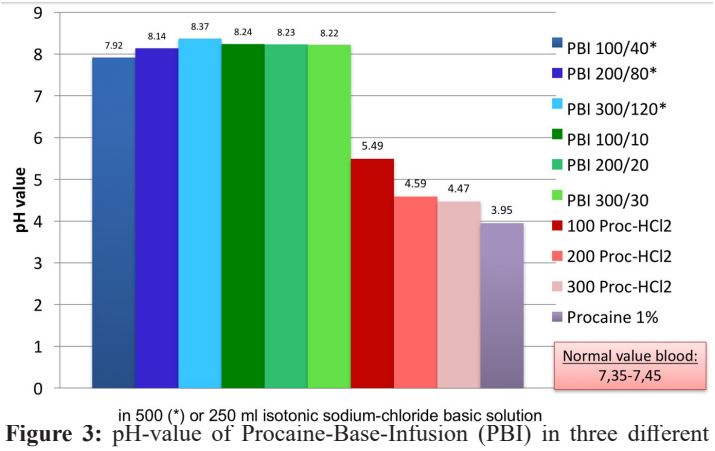

Figure 3: pH-value of Procaine-Base-Infusion (PBI) in three different concentrations, base mixture (1,68%) and pure Procaine-Hcl.

Examples from treated patients

The following case reports shall underline the various possibilities to use the method in different kinds of diagnosis:

Case 1

juvenile rheumatoid arthritis: patient H.R., 34 years old, started with 3 years, ellbow, ankle, MCP hands, knees, Iritis

State before (9th August 2016): knee swelling right, joint pain in knees, shoulders and ankles, many years MTX and Remicade®, Prednison and NSAR in intervals, would like to come away from pharmaceutical drugs, will change her lifestyle completely, RF positive, CRP 61 mg/l, aBGA: pH: 7.42, BE: - 2.1 mmol/l, Vitamin A and D low, anemia

Therapeutic procedure: first series (10x) Procaine-Base-Infusion (PBI) weekly (titration till 300 mg Procaine and 100 ml 8,4% Na-bicarbonate), due to much better general condition continuation of infusion twice per month

Additional complementary treatment: change of diet (vegetarian), supplementation with Bosvay® 3x500 mg, Antioxidant complex, Epogam omega 6, Omni Biotic stress repair®, Vitamin D3 3000 IU, Vitamin A, Chlorella 3x3 tabl., Solidago comp. 3x3 drops

Follow up: very fast reduction of pain, stiffness and joint swelling, very good general condition, has stopped conventional medication after 8 weeks, QBC normal

Last Consultation 21.9.2017: "I am very happy, all my problems are approximately 95% better, no more swelling of the knee, I am delighted, and since three weeks I am sure: I am pregnant!".

Case 2

deep Foot Ulceration and chronic Osteomyelitis: patient H.S, 56 years old, state after kidney transplantation, cytostatic therapy (see figure 4a-c)

State before Procaine treatment (17th April 2009): all together 12 (!) operations during four months stay at the university hospital, multiple rejection reactions after autologous skin transplantations, wound healing disorders on harvesting points, CRP 98,5 mg/l, highly inflammatory ulceration of the dorsum of foot, partly extensor tendons and bones are visible, buffy test with metabolic

acidosis,

Therapeutic procedure: 2x per week Procaine-Base-infusion (titration till 500 mg Procaine and 120 ml 8,4% sodium bi-carbonate),

Follow up: 25.5.09: CRP: 23.3 mg/l, wounds on forearm and upper leg completely healed, ulceration foot 80% closed, pain reduced from VAS 8 to 2-3, Opioid drug (Tilidin ret. 200 mg) discontinued, 17.6.09: CRP: 6.8 mg/l, foot wound also complete dry, increase of motion training, 4.10.09: maintenance dose 1 tablet ProcClusterR 50 mg, very beneficial, no recurrence till today,

Additional complementary treatment: exposure to ozone gas locally (two month), homeopathic remedies, anti-oxidative acting supplement complex, alkaline-rich and hypo-allergic food.

Comment: Together with the anti-inflammatory and vasodilating features of procaine the known problem of metabolic alkalosis in patients with chronic kidney diseases and after transplantation can be solved by the combination with sodium bi-carbonate [92,93].

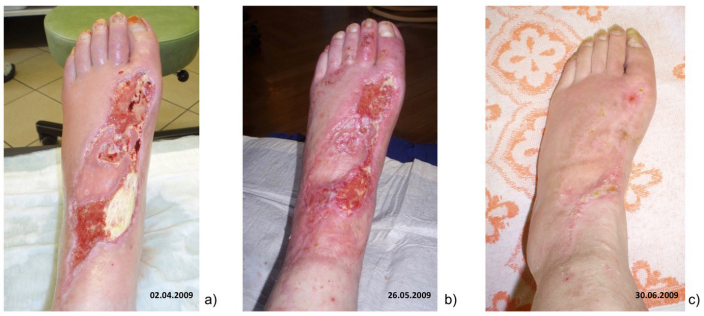

Figure 3: Follow up of the case two.

Case 3

psoriatic Arthritis: patient R.N, 60 years old, suffering from psoriatic arthritis since ten years, additional symptoms are chronic fatigue, depression, hypertension, sleep apnea

State before Procaine treatment (11th November 2016): diffuse muscle cramps and pain permanently between VAS 6-7 despite complex medication (Sirdalud®, Relaxane®, Ibuprofen, Prednisolon 12,5 mg, Novaminsulfon (2x500 mg), Otezla® 60 mg), awkward gait with two crutches, intensive pain and reduction of movement left shoulder, hip and metacarpophalangeal joints both sides, CRP 41 mg/l, aBGA: pH: 7.43, BE: 2.1 mmol/l

Therapeutic procedure: first series (10x) PBI twice a week (titration till 400 mg Procaine), due to much better general condition continuation of infusion weekly

Follow up: Stepwise reduction of pain till VAS 1-2, successful reduction of pain medication to the half amount including Otezla®, much better general condition, mood distinct brightened, energy feeling significantly better, swelling and restriction of movement in affected joints marked improved, control CRP < 5 mg/l, after 20 Procaine infusions the patient is almost painless, happy, has stopped using NSAR and Otezla®

Additional complementary treatment: start with alkaline-rich nutrition, supplementation with Vitamin E (800 IE) and antioxidant complex, frankincense (Bosvay®,3x800 mg), Harpagophytum (3x480 mg)

Comment: The positive effect of neural therapy and intravenously injected procaine is mentioned in old literature [94].

Case 4

Sclerodermia: patient H.S., 48 years old, disease started in 2010, State before Procaine treatment (19th March 2011): joint pain, coldness of fingers, dysaesthesia, dry eyes

Therapeutic procedure: six weeks PBI with increasing dosage, after two months changeover to PBI monthly

Follow up: has a good effect meanwhile over a period of six years Additional complementary treatment: change of diet, removal of amalgam and appropriate detox, probiotics for intestinal health.

Conclusion and Outlook

After the empirical start twenty years ago the Procaine-Base-infusion treatment meanwhile reached a well-accepted level of clinical importance and has advanced as routine therapy in many hospitals and outpatient departments for pain treatment, rehabilitation and natural medicine. Even if scientific findings convincingly confirm the Procaine-Base mechanism of action, spectrum of indications and the individualized application, more research and scientific studies are warranted.

It is very important for the authors of this article to emphasize that the treatment method of Procaine is conducted properly, especially to individualize the therapy according to the acid-base-homeostasis and clinical parameters of the patient [95]. Finally, it is noticeable that the method is not a replacement for neural therapy injections, especially for treatment of neuro-modulative triggers.

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