Neuropathic pain in diabetic nephropathy—update on analgesic strategies

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Introduction

Diabetic neuropathies may impair quality of life, they are both prognostically and pathogenetically important factors for the development of the diabetic foot syndrome and associated with a reduced life expectancy. Improvement of metabolic control over the years has been proven to reduce the incidence of diabetic neuropathy in type 1 [1] and presumably also in type 2 diabetic patients [2,3]. In the near future, besides intensified diabetes treatment, metabolic steps important in the pathogenesis of diabetic neuropathy may be targeted by specific drugs effectively inhibiting the accumulation of sorbitol, reducing oxidative stress, stopping the formation of advanced glycation end products, improving nerve blood flow, reversing changes in membrane lipid metabolism, or substituting nerve growth factors. At present, and in the foreseeable future, it seems to be impossible to completely eliminate the development of neuropathic diabetic lesions because normoglycaemia is achieved in only a small part of all patients. This implicates that neuropathy will remain a clinical problem for the years to come. Besides intensive treatment of diabetes which is indicated in all patients at risk, additionally symptomatic treatment is necessary in some patients with neuropathic pain. The prevalence of symptomatic distal symmetrical polyneuropathy, being the predominant cause of neuropathic pain in diabetic patients, ranges from 20 to 40%. The proportion of patients suffering from pain not treatable with simple analgesics and thus requiring specialized care is largely unknown. Since diabetic micro- and macroangiopathic complications cluster in patients, it is the patient with diabetic nephropathy who is particularly in need of treatment for neuropathic pain.

How to compare different drugs?

The choice of an adequate treatment for neuropathic pain should take into account proven efficacy, number and severity of adverse events, toxicity, pharmacokinetics, contraindications, limitations for treatment due to comorbid conditions, and—last not least—costs. Obviously, it is difficult to compare all these variables for the drugs to be described later, since there is no common denominator for efficacy, and only in rare instances have different drugs been compared directly. A rough estimate of efficacy may be the number of patients needed to treat (NNT) to obtain a substance specific beneficial effect in one patient [4]. Direct comparisons are, however, hampered by the fact that NNT’s are derived from studies with different durations of drug treatment and with different endpoints which may not be directly comparable. The relevance of the NNT is further weakened by the fact that due to the small number of patients included in most studies, the 95% confidence intervals are sometimes extremely large. Consequently, the differences of NNT’s for different substances that have been found are frequently not statistically significant. Clearly, in clinical practice, the apparent response to a given drug is much better than indicated by the NNT, because not only specific but also unspecific effects including placebo effects are observed [5].

Physical measures

As the first step in treating neuropathic pain it is useful to apply physical measures even though the effects of application of creams, massage, and cold and warm applications are difficult to quantitate. Acupuncture and transcutaneous electrical neural stimulation have been tested in a few trials and despite the difficulties in designing really controlled, blinded studies, are believed to provide specific relief of pain.

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Normoglycaemic metabolic control

Normalization of hyperglycaemia is recommended for the treatment of pain based on the results of uncontrolled clinical studies [6,7], anecdotical evidence and animal experiments. Systematic controlled trials to prove this effect have not been performed. A comparably large number of anecdotical reports describe painful symptoms after rapid improvement of metabolic control. Regrettably, pain reduction was not measured as an outcome in the large clinical trials which aimed to quantitate the effects of near normalization of glycaemic control on the development of late complications. Moreover, in most studies of combined pancreas–kidney transplantation the effect of normoglycaemia on symptoms, especially on pain, was not investigated [8]. Since normalization of glycaemic control has been proven to reduce the incidence of neuropathic lesions in type 1 and type 2 diabetic patients, it should certainly be part of the treatment programme.

Tricyclic antidepressants

Tricyclic antidepressants, e.g. imipramine, amitriptyline, clomipramine and desipramine, have been investigated in randomized, placebo-controlled, cross-over trials of 2–6 weeks duration with mean doses around 75–100 mg/d. NNT’s were found to be 1.3–5, the NNT to get one adverse event, the ‘NNH’ (number of patients needed to harm), was about 2 [9]. Since the plasma half-life of all tricyclic antidepressants is rather long (12–22 h) it is prudent to increase the daily dose no more frequently than on a weekly basis. Besides the well known side effects of tricyclic antidepressants (sedative, anticholinergic, orthostatic, cardiac and convulsive effects, and weight gain) which vary between the above mentioned substances one should keep in mind that the use of these substances increases the incidence of hip fractures [10] and suppresses heart rate variability. The long term impact of this change in autonomic tone on life expectancy is not known. The combination of tricyclic antidepressants with neuroleptic drugs has not been proven to be superior to the monotherapy.

Selective serotonin reuptake inhibitors

The number of trials to prove the efficacy of selective serotonin reuptake inhibitors for pain treatment in diabetic patients is rather small. Paroxetine and citalopram (40 mg/d each) revealed NNT’s of 2–5 whereas fluoxetine had no significant effect compared to placebo. These substances are better tolerated, have less significant side effects and do not suppress heart rate variability, but surprisingly also increase the incidence of hip fractures [10].

Anticonvulsants

Anticonvulsants were introduced into the treatment of neuropathic pain in the sixties based on uncontrolled trials. The first substance was diphenylhydantoin (300 mg/d), the beneficial effect of which has not been unequivocally proven. Carbamazepine (600 mg/d) was investigated more intensively and was found to be effective. The NNT is 2–4, the NNH 2–5 [11]. Recently, gabapentine has been investigated. The daily dose in most patients was 3600 mg though the mean effective dose may be much lower. Gabapentin has been shown to significantly reduce neuropathic pain in diabetic patients (NNT 4, NNH 5) [12].

Antiarhythmic drugs

Antiarrhythmics (a single dose of 5 mg/kg lidocaine i.v. or daily doses of 450–600 mg mexiletine orally) have been investigated in diabetic patients. Mexiletine did not influence all endpoints in all trials. In retrospective evaluations, its effect was best on stabbing, heat and burning sensations [13]. The NNT was about 2 if a significant effect was observed. The NNH was 5–10. Since mexiletine may have proarrhythmic effects it is problematic to use this substance in diabetic patients with macroangiopathic complications. In the reported trials cardiac adverse events were not observed, but given the small number of patients investigated this does not exclude substantial side effects.

Capsaicin

Contrary to all drugs described which are used systemically and therefore lead to systemic side effects, capsaicin, a chili pepper ingredient, topically applied four times daily as a 0.075% cream, may reduce neuropathic pain in diabetic patients. The NNT is 3–5, the NNH is 2–3 [14]. The effect achieved is comparable with that of amitriptyline [15]. The high rate of adverse events is caused by the initially increased pain sensation in the creamed areas, the unintentional contamination of mucous membranes like conjunctivae, and the inhalation of dried cream particles. Systemic adverse events do not occur although long term toxic effects on nerve endings are not yet totally excluded.

α-Lipoic acid

In Germany, α-lipoic acid (daily 600–1200 mg/d i.v.) was shown to effectively reduce pain in diabetic patients [16]. The NNT was 4–5. Adverse events were not observed in the group treated with 600 mg and were negligible in the group treated with 1200 mg. It remains to be seen whether oral treatment may be equally effective and how long the effect may remain stable.
after cessation of therapy. Ongoing studies will soon answer these questions.

Opioids

Although opiates and opioids are believed to be effective means to treat neuropathic pain in diabetic patients, this was not formally investigated before 1998 when tramadol (mean effective dose 210 mg/d orally) was shown to be superior to placebo [17]. Fentanyl was shown to be effective in neuropathic pain syndromes. This study, however, did not include diabetic patients.

Miscellanea

A large number of other substances including aldose reductase inhibitors, ω-linolenic acid, dextromethorphan, nonsteroidal antiinflammatory drugs, vitamins, vasodilators, calcitonine and clonidine have been investigated with results precluding clear recommendations.

Treatment in nephropathic/neuropathic diabetic patients

How should the results from these randomized clinical trials be applied to the subgroup of diabetic patients with end-stage renal disease who were never included in these studies? In such studies impairment of renal function, like other diabetic micro- and macroangiopathic complications, were exclusion criteria. As a result it remains unclear whether—and if, how—these results are applicable in daily practice to a presumably large number of patients requiring drug treatment. Published treatment algorithms do not take into account increased cardiovascular risks, concomitant diseases or co-medications. One must bear in mind that with regard to efficacy, evidence from randomized clinical trials does not support a clear-cut predominance of one of these substances. As a result other criteria become important for the selection of the appropriate treatment. Among others one has to take into consideration number, severity and type of adverse events (including cognitive impairment which may influence the ability to drive vehicles), contraindications, limitations of use in particular patients, pharmacokinetic characteristics and costs.

Looking at contraindications and comorbid conditions first, tricyclic antidepressants do not seem to be a prudent choice in those patients in whom cardiovascular diseases and disturbances of the autonomic nervous system may be prevalent, and the same may be true for carbamazepine and mexiletine. Selective serotonin reuptake inhibitors, capsaicin, ω-lipoic acid, gabapentin and tramadol may have certain advantages. Impairment of renal function may be a limitation for mexiletine and gabapentin, the dose of which should be carefully adjusted to residual renal function. Cognitive impairment may be expected in patients treated with tricyclic antidepressants, mexiletine and gabapentin. Looking at costs of treatment, in Germany they are lowest for tricyclic antidepressants and carbamazepine, followed by mexiletine, capsaicin, gabapentin and selective serotonin reuptake inhibitors and are highest for ω-lipoic acid. Last not least, medicolegal considerations should be mentioned: most substances are not approved for the treatment of neuropathic pain by national regulatory authorities. Doctors should inform their patients thoroughly about the substance used, obtain informed consent, and watch carefully beneficial effects and adverse events.

References

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Note added in proof

One large study has now been published [18] whereby the authors state that in this study there was 'no effect on neuropathic symptoms (of the treatment with alpha-lipoic acid) distinguishable from placebo to a clinically meaningful degree'.