Journal of Clinical & Translational Endocrinology 4 (2016) 53–58

Contents lists available at ScienceDirect

Journal of Clinical & Translational Endocrinology

journal homepage: www.elsevier.com/locate/jcte

Original Research

The chlorite-based drug WF10 constantly reduces hemoglobin A1c values and improves glucose control in diabetes patients with severe foot syndrome

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ARTICLE INFO

Article history:
Received 11 March 2016
Accepted 2 May 2016

Keywords
Foot ulcers
Healing
WF10
HbA1c
Diabetes

ABSTRACT

Aims: The intravenous application of the chlorite-based drug solution WF10 is known to improve wound healing in patients with diabetic foot syndrome. In this retrospective study, we addressed the question, which effects are caused by this drug in patients with diabetic foot ulcers on the hemoglobin A1c value.
Methods: Patients received five consecutive daily infusions of WF10. Three patients received a second cycle of WF10, and one patient a third cycle.
Results: On a group of twelve patients with diabetic foot syndrome, WF10 gradually reduced the HbA1c values from a high-risk range (9.1 ± 1.6% (76 ± 13 mmol/mol)) into a low-risk range in all patients but one. These values remain low over at least 8 to 12 weeks after the administration of WF10. This drug improved also considerably wound healing processes in eleven patients.
Conclusions: The chlorite component of WF10 is known to inactivate efficiently free cytotoxic hemoglobin forms that might accumulate in peripheral blood after hemolysis and induces the removal of predamaged red blood cells from circulation. By these mechanisms WF10 diminished toxic effects of hemolysis, improved microcirculation and glucose consumption in affected tissues, and prevented, thus, below knee amputation.

Introduction

Diabetic foot syndrome (DFS) is a severe pathology of diabetes mellitus type 1 and 2 and is associated with a 12-month mortality of 16.7%, which doubles after major amputation [1]. The risk for this and other common complications of diabetes like retinopathy, nephropathy, cardiovascular disease and others increases with enhanced values for hemoglobin A1c (HbA1c) [2], an important parameter for the long-term harm of hyperglycemia. Elevated HbA1c values are known to decrease the wound healing rate in neuropathic foot wounds and in those with peripheral artery disease [3].

The enhanced, insulin-independent uptake of glucose by erythrocytes favors the glycation of their proteins, impairs the deformability of these cells, and contributes to an osmotic stress by conversion of glucose into sorbitol via aldose reductase [4–6]. Hence, the impermeable sorbitol decreases the mechanic fragility of red blood cells and favors hemolysis [7]. There is a clear relationship between hemolysis degree and fasting plasma glucose concentrations as well as the HbA1c value in patients suffering from diabetes mellitus type 2 [8]. Otherwise, hemolysis diminishes the bioavailability of nitric monoxide (NO) and decreases, thus, blood circulation in affected tissues [9]. There is also a general association between enhanced glucose concentrations and decreased NO availability in diabetes [10,11]. In these patients, hemolysis is also linked to an enhanced thrombotic risk [12,13]. In their blood, the non-enzymatic modification of fibrinogen leads to the formation of complexes between fibrin fibers and red blood cells and to a changed morphology of these cells [14].

The chlorite-based drug solution WF10, which is given to patients in form of an intravenous infusion, has successfully been applied to improve the clinical outcome in patients with diabetic foot ulcer syndrome [15,16]. This adjunct therapy to standard diabetes treatment significantly accelerated the wound healing process and reduced the rate of foot amputation. However, effects of this therapy on glucose status and especially on the long-term behavior of the HbA1c value remain unknown.

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http://dx.doi.org/10.1016/j.jcte.2016.05.001

To deepen our knowledge about the beneficial action of WF10 in diabetic patients with foot syndrome, we addressed here the question whether the administration of WF10 improves besides the clinical outcome also important parameters of glycemic control. On twelve DFS patients, WF10 caused a normalization of enhanced HbA1c values. Follow up of a comparable group of diabetic patients with DFS, which were subjected to conventional wound care therapy, revealed no such reduction in HbA1c values [17].

Patients and methods

Patient's characteristics at baseline

This retrospective study was undertaken from March 2015 to December 2015 on diabetic patients with foot ulcers at a wound care clinic, Surgery Department of the General Police Hospital, Bangkok, Thailand. These patients received WF10 treatment in an attempt to treat diabetic foot ulcer and prevent below knee amputation (BK). The data of demographic, coexisting medical conditions, wound staging, and the glycemic control data before and after treatment were reviewed.

This study was approved by the ethical committee of the General Police Hospital, Bangkok, Thailand.

Assessment of wounds

Patient's ulcer were assessed and classified into different grades and stages according to Wagner's Grading System [18]. Grade 0 corresponds to intact skin, grade 1 to superficial diabetic foot ulcer, grade 2 to extensive ulcer involving ligament, tendon, joint capsule, or fascia without abscess or osteomyelitis. The higher wound grades correspond to deep ulcer with abscess or osteomyelitis (grade 3), gangrene to portion of forefoot (grade 4) or extensive gangrene of foot (grade 5).

Ulcers were graded as infected or not on the basis of the presence or absence of purulent discharge together with other local signs (warmth, erythema, lymphangitis, lymphadenopathy, edema and pain) and confirmed with swab wound culture. Diagnosis of osteomyelitis was made on the basis of radiological findings.

Determination of parameters of glucose metabolism

Hemoglobin A1c testing was performed by Integra 400 (Roche Diagnostics, Laval, QC, Canada). Fasting blood glucose level was performed daily by Dextrostix (Dtx) with a Glucocheck meter. Blood chemistry tests were performed by the Siemens Advia 1800 analyzer. Complete blood count was performed by Beckman Coulter hematology analyzer.

Treatment protocol with WF10

Five consecutive infusions of WF10 (referred to as 'cycle') at a dose of 0.3 ml/kg body weight, diluted in 500 ml physiological saline, were administered to DFS patients in an attempt to prevent BK and to induce healing of the chronic ulcer. As the primary focus was on wound healing, in three patients (NP, PS, SA), a second cycle of WF10, and in one patient (SR) after two cycles at 0.3 ml/kg even a third cycle at 0.5 ml/kg body weight were deemed clinically beneficial and consequently administered.

The usually administered WF10 dose of 0.3 ml/kg was lower than the recommended dose of 0.5 ml/kg. Probably in cases of NP, PS, and SA a selected dose of 0.5 ml/kg body weight for the first cycle may have lessened the need for another treatment cycle.

Results

Patient's characteristics during treatment with WF10

This retrospective study was undertaken from March 2015 to December 2015 on twelve diabetic patients with severe foot ulcers with gangrened toes and suspected osteomyelitis. These patients received WF10 treatment in an attempt to prevent below knee amputation (BK) at the General Police Hospital, Bangkok, Thailand. Baseline characteristics of these patients at hospitalization are summarized in Table 1.

For eight patients, BK had been recommended by physicians from transferring hospitals. All patients had been diabetics for an average of 16 years and were associated with hypertension. Six patients had cardiovascular disease and three dyslipidemia. Two patients received insulin treatment and ten received only oral anti-diabetic medications prior DFS treatment. Based on this standard of care patients exhibited mean fasting glucose values of 202.8 mg/dl (107 mg/dl–332 mg/dl) and mean HbA1c levels of 9.1% (6.9%–11.5%) at baseline. Ten patients had been anemic (hematocrit less than 35%). Two patients exhibited peripheral occlusive disease symptoms. The glomerular filtration rate (GFR) for four patients were at or below 60 ml/min. Platelets of eight patients had been elevated.

Upon treatment with WF10, clinically all patients but one (SA) have shown either complete healing of their wounds or at least improvements by two points on the Wagner Score. Clinical parameters of the twelve diabetics, time to complete healing, medications against diabetes mellitus, and blood transfusions are summarized in Table 2.

Clinically a visible improved blood circulation in affected tissues could be seen, granulation developed like a manicured lawn. Kidney function remained stable for at least six months. Elevated platelets became normal.

Alterations in glucose status upon WF10 treatment

In all patients but one (SR), the HbA1c level gradually declined from high risk levels (9.1 ± 1.6%) to low risk levels of 6. 7 ± 1.4% at week 4, and 6.2 ± 1.1% at week 8 after five consecutive daily infusions of WF10 (Table 3). The mean value of 6.8 ± 1.0% at week 12 was also considerably lower than the baseline one, but slightly higher than the value at week 8. A mean HbA1c value of 7.3 ± 1.5% (n = 7) was determined at week 16. Statistical analysis applying the unpaired Student's t-test revealed a significant decrease of HbAc1 data in comparison to the baseline values with $p < 0.001$ (week 4, week 8), $p < 0.01$ (week 12), and $p < 0.05$ (week 16).

Individual data for alterations of HbA1c values are given in Fig. 1. HbA1c declined during treatment from high risk into low risk range for at least eight and up to twelve weeks. Patient SR did not respond during the first two cycles of WF10, but after receiving the recommended dose of 0.5 ml/kg in the third cycle HbA1c declined to 7.3% at week 12 and further to 6.9% at week 16 (Table 3).

Fasting glucose control improved after WF10 treatment (Table 3). Additionally the amount of oral hypoglycemic drugs and insulin required before and during treatment were gradually reduced and fasting glucose remained at a level of around 150 mg/dl for at least eight weeks.

Hematocrit and anemia control

WF10 induced an accelerated splenic clearance of dysfunctional erythrocytes bearing high levels of HbA1c. Patients with the highest HbA1c levels experienced the highest reduction. Expectedly, a transient drop in hematocrit values during the infusion period has been observed accompanied by a compensating erythropoiesis. As found earlier in healthy individuals and in virus infected patients,