Comparison between nasal and intravenous desmopressin for the treatment of aminosalicylic acid-induced platelet dysfunction

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Summary

Background and objective: The study was conducted to compare the standard intravenous route with the intranasal route of desmopressin application and to establish the best time for initiating treatment with desmopressin with the use of the Born test and the PFA 100®-Analyzer for monitoring the therapeutic effect.

Methods: Thirty healthy volunteers (ASA I) with no known bleeding disorder were randomly assigned to an intravenous or an intranasal group in a cross-over design fashion. After obtaining baseline values, the volunteers were given 500 mg aminosalicylic acid for 3 days. On day 4, platelet function tests were performed and desmopressin (0.3 µg kg⁻¹ body weight) was administered either intravenously or intranasally. Born tests (aggregation after stimulation with epinephrine and collagen) were conducted at 30 and 240 min, and PFA 100® bleeding time measurements were conducted at 30, 120 and 240 min after desmopressin administration. Wilcoxon signed rank sum tests or non-parametric ANOVA for repeated measures were used for statistical evaluation.

Results: All volunteers showed a marked decreased platelet function in the Born test (especially if stimulation with epinephrine was used) and an increased PFA 100® bleeding time after treatment with aminosalicylic acid. Platelet function was improved by intravenous as well as intranasal application of desmopressin (P<0.001) after 30 min. The effect diminished after 4 h in both groups.

Conclusions: Intravenous as well as intranasal desmopressin improved platelet function in healthy volunteers with aminosalicylic acid-induced platelet dysfunction at least 30 min after application. The effect lasts up to 4 h.

Keywords: HAEMATOLOGICAL TESTS, platelet function tests, bleeding time; HAEMOSTASIS, platelet activation, platelet aggregation; HAEMOSTATICS, desmopressin; SALICYLIC ACIDS, aminosalicylic acid.

Introduction

Desmopressin (DDAVP) is commonly used to treat congenital [1–5] or acquired [6,7] bleeding disorders based on platelet dysfunction. With the widespread use of drugs such as aminosalicylic acid as a secondary prophylaxis for arterial thrombosis, the risk of bleeding complications due to aminosalicylic acid-induced platelet dysfunction becomes a topic of clinical importance for anaesthesiologists and surgeons. There are several reports about the successful treatment of aminosalicylic acid-induced platelet dysfunction with desmopressin [8–11] that indicate an optimal dose of 0.3 µg kg⁻¹ body weight intravenously (i.v.). Now that highly concentrated nasal spray (Octostim®) is commercially available in Germany, comparable doses can be given by a non-invasive route. The
authors conducted this open study with healthy volunteers, first, to compare the effects of nasally with i.v. administered desmopressin on aminosalicylic acid-induced platelet dysfunction and, second, to find an optimal time for the application of desmopressin regarding the improvement of platelet function. Case reports and small-scale investigations suggest a peak effect after 30 min [12] and there is limited information about how long the effects of desmopressin last [13] either from clinical experience or half-life based estimations.

**Methods**

The study was conducted with 30 healthy volunteers (ASA I), of whom 17 were females, after approval by the Institutional Review Board of the Medical Faculty of the University of Aachen and with the written informed consent of the participants. Participants’ mean body weight was 70.6 (range 51–112) kg. The volunteers (non-smoking individuals with no history of bleeding disorders, thromboembolism or use of other drugs in the last 4 weeks) were randomly assigned to the i.v. or intranasal group by a computer-generated block randomization list and received both methods of application in a cross-over design with at least 6 weeks’ recreation between the two test cycles.

Platelet function was analysed from citrate blood samples by aggregation testing with the Born method [14,15] using an APACT® (APACT, Rostock, Germany) aggregometer and computer system and commercially available test solutions containing collagen (10 µg mL⁻¹) or epinephrine (50 µmol L⁻¹).

PFA 100® bleeding times were measured using citrate blood samples and the PFA 100® Analyzer (Dade Behring, Schwalbach, Germany) with collagen/epinephrine (col/epi) and collagen/ADP (col/ADP) cartridges for stimulation of the plug-formation process [16]. Each col/epi cartridge contained a membrane with 2 µg equine Type 1 collagen and 10 µg epinephrine bitartrate. Each col/ADP cartridge contained a membrane coated with 2 µg equine Type 1 collagen and 50 µg adenosine-5’-diphosphate (ADP).

After baseline values of platelet function and PFA 100® bleeding time had been obtained, all volunteers received 500 mg oral aminosalicylic acid (Aspirin®) for 3 days and were tested again on the fourth day. Then they were randomly assigned by a computer-generated block randomization list to receive either 0.3 µg kg⁻¹ body weight desmopressin (Minirin®) i.v. as infusion over 30 min or two puffs (each puff containing 150 µg desmopressin) of the nasal spray (Octostim®) in accordance with the manufacturer’s dosage recommendation. Those who received i.v. desmopressin in the first run were in the intranasal group in the second run and vice versa with at least 6 weeks’ recovery time between both studies.

Born tests were performed once after 30 min and again after 240 min. PFA 100® bleeding times were measured 30, 120 and 240 min respectively after either the infusion was stopped or the nasal puffs were given.

Volunteers were discharged from the test centre after obtaining the final blood sample and a physical examination to exclude side-effects. All volunteers were contacted by telephone after 24 h and questioned with regard to delayed side-effects (such as peripheral oedema formation).

**Statistical analysis**

Because there was a wide range of normal varieties in platelet function between individuals, we did not use absolute numbers but calculated all values generated from Born tests (after treatment with aminosalicylic acid, 30 and 240 min after desmopressin) as a percentage of baseline values (obtained before administration of aminosalicylic acid) using the maximal amplitude as parameter.

PFA 100® bleeding times are given in seconds (absolute numbers) as mean with standard deviation (SD). The Wilcoxon signed rank sum test or non-parametric ANOVA for repeated measurements were used as necessary for statistical analysis using a significance level of \( P < 0.05 \). Intragroup analysis and intergroup comparisons were performed separately.

**Results**

Figure 1 shows a significant (\( P < 0.001 \)) improvement of platelet function (stimulation with epinephrine in the Born test) 30 min after desmopressin administration both in the i.v. and the nasal groups. After 240 min, platelet dysfunction deteriorated (defined as a reduction of aggregation compared with the maximum treatment effect of \( > 20\% \)) in 80% of the i.v.-treated volunteers, while 46% of the nasal group still showed a significantly improved platelet dysfunction after aminosalicylic acid therapy with improvement after desmopressin was also significantly detectable (\( P < 0.05 \)) when stimulation with collagen in the Born test was used. There was no significant difference between the nasal and the i.v. groups in the ANOVA whatever stimulant was used.

Figure 2 shows the PFA 100® bleeding times (stimulation with col/epi), which were significantly
(P < 0.001) improved 30 and 120 min after desmopressin administration in both groups without a significant difference between i.v. or intranasal administration. Compared with the reference values of the manufacturer (Dade Behring, Germany), in vitro bleeding times were pathologically elevated after aminosalicylic acid in 93% (nasal group) and 86% (i.v. group) of the volunteers, but returned to normal in all i.v.-treated volunteers and in 93% of those in the nasal group. After 4 h, the PFA 100® bleeding times of 46% in both groups were still within the normal range.

PFA 100® bleeding times measured with col/ADP (Fig. 2) were only slightly prolonged by aminosalicylic acid and would be classified as pathological in 20% of the volunteers, but they also showed a significant (P < 0.05) response to desmopressin treatment.

We had three volunteers with normal PFA 100® bleeding times but a marked reduction of platelet function in the Born test after aminosalicylic acid. These data indicate a sensitivity of the in vitro bleeding time with col/epi (PFA 100®) to detect aminosalicylic acid-induced platelet dysfunction compared with the Born test of 90% in our sample.

All volunteers experienced some skin flush, predominantly facial, after desmopressin by whichever form taken. One female volunteer in the i.v. group developed peripheral oedema (increase of the total body weight from 51 to 54 kg) during 24 h after the administration of desmopressin and required a single treatment with furosemide 10 mg i.v.

**Discussion**

Desmopressin improves platelet function by means of a marked increased plasma level of Factor VIII and von Willebrand factor. Moreover, the expression of
tissue factor on the surface of endothelial cells is increased and a direct stimulation effect on the platelet membrane to improve contact aggregation is discussed [11]. These pharmacodynamic mechanisms indicate that the existence of a minimum population of functioning platelets is a condițio sine qua non for desmopressin therapy to be effective [6]. The elimination half-life of desmopressin is 3.5–4.5 h, with a peak effect of von Willebrand factor release after 30 min. There might be a tachyphylactic effect after repeated administration [17], although other studies show a similar response after a repeated i.v. dose 3 h after the first administration [18], or no further reduction after the third dose while a second proved to be 30% less effective than the first [19].

A positive effect of desmopressin on platelet function has also been shown for other modes of drug-induced platelet dysfunction including ticlopidine [20]. Theoretically, it should also be effective with clopidogrel but not with abciximab, which is a monoclonal antibody with the ability to block the GIIb/IIIa receptor. These GIIb/IIIa receptor complexes are the final step in the platelet aggregation–signaling chain, so even the highest concentrations of Factor VIII and von Willebrand factor are unable to stimulate the blocked receptors.

Besides our original objective to look for differences between the nasal and i.v. routes of desmopressin application, we found the Born test with epinephrine superior in detecting aminosalicylic acid-induced platelet dysfunction compared with collagen. PFA 100® bleeding times are only valuable in the detection of aminosalicylic acid-induced platelet dysfunction if stimulation with epinephrine is used, while stimulation with ADP proved unreliable for this indication. PFA 100® bleeding times were still significantly improved after 4 h, whereas the platelet function tests with the Born method once again showed significant dysfunction. These differences and the fact of wide ‘normal’ ranges given by the manufacturer might limit the usefulness of the PFA 100® bleeding time for monitoring the therapeutic effect of desmopressin treatment and should be evaluated in a larger trial on surgical patients with blood loss as a variable to indicate clinical significance.

Our data demonstrated that the intranasal route using highly concentrated nasal spray (Octostim®) is equally effective in reducing PFA 100® bleeding times and improving platelet function in the Born test for treating aminosalicylic acid-induced platelet dysfunction compared with the standard i.v. route. In both groups, we showed a significant effect 30 min after desmopressin administration. This would be a net time benefit of 30 min from the start of the treatment to the effect in the nasal group because a more rapid i.v. infusion is not recommended by the manufacturer. It might lead to an increase of flush reactions and vasodilatation.

Another side-effect is a short-term increase of fibrinolytic activity after desmopressin application before improvements of platelet function and haemostatic function occur.

Our in vitro data also suggest a clinical effective time frame of between 30 and at least 120 min, and sometimes up to 240 min, whichever way of administration is used. There was a trend towards a longer lasting effect (Born test) in the nasal group that, however, did not reach statistical significance. One explanation for the prolonged effect of nasal desmopressin might be a slower absorption rate and a later peak effect of the increase in plasma concentrations of von Willebrand factor and direct platelet activation.

Although the relative dose on a per kilogram basis in the nasal group was in most cases higher than in the i.v. group, we did not see any correlation between weight-corrected doses and the treatment effects.

Limitations of the study

Endpoints like PFA 100® bleeding time and platelet function measured were chosen with the Born test to define the effects of aminosalicylic acid and desmopressin treatment on platelet function because the decision for prophylactic treatment is mostly guided by those tests and patients’ history. We did not measure Factor VIII or von Willebrand factor concentrations as direct indicators of desmopressin effects, so we cannot comment on the correlation between those values and the observed effects on platelet function and PFA 100® bleeding time. This might be part of a further study with closer blood sample intervals to define the exact time of the peak effect after nasal administration of desmopressin. We can also make no comments about the correlation of the treatment effect observed with our surrogate variables and the reduction of blood loss or bleeding complications in a specified procedure because we did not perform surgery on our volunteers.

Conclusion

Desmopressin significantly improves platelet function in volunteers with aminosalicylic acid-induced platelet dysfunction after 30 min when given via the i.v. or intranasal routes. There is a net time reduction of 30 min from the time of drug administration to its effect if given intranasal compared with the standard infusion regimen recommended by the manufacturer that might be modified by different centres. The effective time frame seems to be between 30 and 120 (up to 240) min.
The Born test with epinephrine and the PFA 100® bleeding time with epinephrine should be used to monitor the therapeutic effect of desmopressin in patients with aminosalicylic acid-induced platelet dysfunction.

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References
