References


To the editor:

Use of desmopressin (DDAVP) during early pregnancy in factor VIII–deficient women

Desmopressin (DDAVP) is being used with caution in the first 2 trimesters of pregnancy in women with bleeding disorders1,2 because there is concern that the compound may cause placental insufficiency due to arterial vasoconstriction and increase the risks of miscarriage due to an oxyzotic effect and to maternal and/or neonatal hyponatremia.3 The latter concern is in principle justified because desmopressin is a potent antidiuretic nonapeptide that acts thorough V2 vasopressin receptors.4 On the other hand, its potential for vasoconstriction and uterus contraction is negligible because the compound is practically devoid of these biologic activities related to the activation of V1 vasopressin receptors.5 Evidence of its safety during pregnancy in women with diabetes insipidus is available.6 Since the original description of its use for the treatment of mild hemophilia and von Willebrand disease (VWD), between 1988 and 2002 we used desmopressin in 32 pregnant women with low factor VIII levels in order to improve hemostasis at the time of invasive procedures.

Of 32 pregnant women, 27 were obligatory carriers of hemophilia with factor VIII deficiency, presumably due to extreme random inactivation of their normal X chromosome ( lyonization), and 5 had type 1 VWD. Twenty women underwent chorionic villus sampling at gestational weeks 11 to 12 for prenatal diagnosis of hemophilia, the remaining 12 underwent amniocentesis at weeks 16 to 18 for prenatal diagnosis (7 hemophilia carriers) or karyotyping (5 women with type 1 VWD). In all women, factor VIII levels were low enough to engender an increased risk of bleeding (median, 60 U/dL; range, 40-121 U/dL). In all 32 women there was no abnormal bleeding and in 20 of them pregnancies went successfully to term with the delivery of healthy newborns. In the remaining 12 cases, male fetuses affected by hemophilia on genotyping were aborted under coverage with additional doses of desmopressin. There was no side effect in the treated women other than mild facial flushing and headache and no significant increase in body weight.

This series shows that desmopressin can be used during the first and second trimester of pregnancy and that it is safe during invasive procedures that increase per se the risk of miscarriage. Electrolytes and osmolality were not measured because this is our routine protocol. However, there was no clinical sign of water intoxication or body weight increase in these women, who were warned to restrict fluid intake.

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References


To the editor:

Hyperhomocysteinemia: cause or effect of disease?

We read with interest the article on the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism by Frederiksen et al.1 We do not agree with the hypothesis of the authors that testing C677T MTHFR is an alternative approach to establish if hyperhomocysteinemia is a cause or simply an effect of the disease. Indeed, hyperhomocysteinemia is not a monogenic condition, but a number of acquired and inherited risk factors contribute to its development. Several polymorphisms in the...
Response:

Mendelian randomization suggests that vascular events cause hyperhomocysteinemia, rather than vice versa

We appreciate the comments by Marcucci et al to our recent article.1 In that study, we examined 9238 individuals from the Danish general population of which 1374 and 208 during 23 years of follow-up developed ischemic cardiovascular disease (ICD) and venous thromboembolism (VTE), respectively; there were an additional 2961 Danes with ICD also enrolled. Plasma homocysteine was elevated 25% in homocysteine levels without an increased vascular risk. This subgroup of patients had mean homocysteine levels of 14.7 ± 0.5 μM, but we do not know how many subjects were hyperhomocysteinemic. Carriers of MTHFR homozygosity had 25% higher homocysteine levels with respect to the other genotypes, but it is unlikely that they were all hyperhomocysteinemic. On this basis, it does not appear reasonable to conclude that homocysteine is an effect of disease.

As homocysteine seems to be implicated in several diseases, it might be plausible that it is simply a marker of disease or of a metabolic derangement in which the leading actor is another parameter still unknown, but the study of Frederiksen et al does not provide the demonstration.

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References


1. Frederiksen J, Juul K, Grande P, et al. MTHFR C677T genotype, like we observed for factor V Leiden genotype.3 Therefore, our data clearly demonstrate the key advantage of Mendelian randomization, that is, avoidance of confounding.2,3

Marcucci et al have a number of questions that we are happy to answer: (1) The subgroup of individuals in which homocysteine levels were measured was simply those attending the 2001 to 2003 examination of the Copenhagen City Heart Study. Any selection bias introduced between this and former examinations is unlikely to influence relative homocysteine levels between genotypes. (2) As the fraction daily taking vitamins did not differ between genotype groups (previous paragraph), vitamin status is unlikely to have confounded our results. (3) As creatinine levels did not differ between genotype groups (previous paragraph), differences in renal function also are unlikely to have confounded our results. (4) Finally, among those with the MTHFR C677T noncarrier, heterozygote, and homozygote genotypes, 15%, 15%, and 30%, respectively, had plasma homocysteine levels higher than 15 μM (Refsum et al5) (chi-square: \( P < .0001 \)).

In conclusion, therefore, because of Mendelian randomization generally avoiding confounding,2,3 we believe that our data suggest that ICD/VTE causes hyperhomocysteinemia, rather than vice versa.

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References

1. Frederiksen J, Juul K, Grande P, et al. Methylenetetrahydrofolate reductase polymorphism (C677T), hyperhomocysteinemia, and risk of ischemic
To the editor:

Serum C-reactive protein parallels secretory phospholipase A2 in sickle cell disease patients with vasoocclusive crisis or acute chest syndrome

Previous studies from our institution have shown that serum secretory phospholipase A2 (sPLA2) levels are markedly increased in sickle cell disease (SCD) patients with acute chest syndrome (ACS) and that sequential measurements of sPLA2 are useful in predicting the subsequent development of ACS in patients hospitalized for vasoocclusive crisis (VOC). However, sPLA2 assays are not widely available in clinical laboratories. Thus, we sought a surrogate marker that might be measured instead of sPLA2. Because sPLA2 is an acute-phase protein, we hypothesized that serum concentrations of another acute-phase reactant, C-reactive protein (CRP), might change in concert with sPLA2. CRP and sPLA2 have been shown to correlate well in patients with septic fever. In addition, CRP values are comparable whether measured in serum or plasma, after delayed sample processing or prolonged storage, or after up to 7 freeze-thaw cycles.

We performed assays for sPLA2 and CRP on 139 serum samples from 20 hospitalized SCD patients; 13 patients had VOC and 7 had ACS. Between 5 and 10 serum samples collected during the course of hospitalization were analyzed for each patient. Serum samples were assayed for sPLA2 on the day of collection, prior to freezing. Enzyme activity was determined with a fluorometric assay and expressed as arbitrary units (AU), where 1 AU was the activity associated with a serum immunoreactive sPLA2 concentration of 100 ng/mL. CRP concentrations were measured with an in-house sandwich enzyme-linked immunosorbent assay (ELISA). To validate the assay, we measured CRP levels in serum obtained from 17 healthy individuals. Serum CRP (mean ± SEM) for this group of donors was 0.81 ± 0.26 mg/L. This concentration is similar to previously published CRP values for healthy donors.

Daily mean serum CRP concentrations and sPLA2 activity during 10 days of hospitalization are shown in Figure 1 and Table 1. Mean CRP values paralleled changes in sPLA2 very closely for the first 5 days of hospitalization, after which they decreased somewhat more slowly than did sPLA2. Examination of plots from individual patients showed that the day of peak CRP concentration coincided with the day of peak sPLA2 concentration in 9 cases, was one day earlier in 5 instances, and one day later in 5 instances. Thus, based on the pattern of changes in concentration, CRP appeared to be a good surrogate for sPLA2.

Table 1. Numerical data for results shown in Figure 1

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<td>sPLA2 mean</td>
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<tr>
<td>sPLA2 SEM</td>
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</table>

In this analysis, we wished only to determine whether CRP could serve as a suitable substitute for sPLA2 in serum samples from SCD patients, and our sole criterion for selecting patients was the availability of several daily serum samples for assay. Therefore, we can draw no conclusions regarding the ability of CRP to predict the likelihood that ACS will develop after hospitalization with VOC. However, changes over time in CRP closely paralleled changes in sPLA2, and values for the 2 analytes were correlated (Spearman rank correlation coefficient = 0.641; P < .0001; data not shown). Overall, these results suggest that further studies should be performed to determine whether CRP could be used as an alternative to sPLA2 to predict the development of ACS in VOC patients.

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