Risk Factors For Prilocaine Induced Methaemoglobinemia Following Peripheral Regional Anaesthesia

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Abstract

Background: The major disadvantage of the local anaesthetic prilocaine is the formation of methaemoglobin with high inter-individual variation. Its underlying causes are poorly understood. Thus, this prospective observational study was performed to identify factors that are associated with increased prilocaine-induced methaemoglobinaemia.

Patients and methods: 162 Patients undergoing major knee surgery under general anaesthesia combined with peripheral nerve blocks received a single bolus injection of 300 mg or 400 mg prilocaine about 30 minutes before surgery via a catheter. Three hours after prilocaine injection, venous blood samples were drawn and methaemoglobin levels were measured. Various variables were recorded and subjected to a stepwise multiple regression analysis.

Results: The mean met-Hb level for all patients was 2.7% (range: 0.9 - 15.4%). A higher dose of prilocaine and younger age were the most important predictive factors for higher methaemoglobin formation. Female sex and to a lower extend the use of high-concentration / low-volume prilocaine also increased methaemoglobin levels. These four factors of the model explain 36% of the total variance. Other investigated factors, including the patient's height, weight, body mass index, the site of catheter insertion, the anaesthetist's judgement concerning the difficulty of catheter placement, duration of catheter placement or an inadvertent puncture of a venous or arterial vessel, had no significant impact on the concentration of methaemoglobin.

Conclusion: The use of prilocaine for regional block is safe since the older patients who might be more susceptible to suffer from clinical symptoms of methaemoglobinaemia usually form less methaemoglobin. However, since prediction of high methaemoglobin levels is far from being perfect, anaesthesiologists performing regional blocks in patients who might be jeopardised by a decrased oxygen transport capacity should continue to use lower doses of prilocaine or switch to another local anaesthetic.

INTRODUCTION

For surgical procedures of the lower limb, plexus blocks and peripheral nerve blocks constitute a widely established analgesic procedure. After placing the nerve catheter it is important to provide fast onset of the block to improve the workflow within the operating theatre. This aim can be reached by using a drug with fast onset. Prilocaine is a medium-long-acting local anaesthetic with a fast onset of action that is comparable with lidocaine and mepivacaine but has a significantly lower systemic toxicity [1, 2]. This is mainly because of a large virtual volume of distribution and a high absorption of the drug in the lung that protects to a great extent against systemic toxic reactions even in case of accidental intravasal injection [3, 4]. Various toxicologic studies showed about 50 % lower blood levels of the drug compared to other fast-onset and medium-long-acting local anaesthetic agents [5, 6, 7]. However, prilocaine bears the disadvantage of the formation of methaemoglobin (met-Hb) induced by its metabolites o-toluidine and nitrosotoluidine [6, 7, 8, 9, 10].

Maximum levels of met-Hb are usually reached 2-4 hours after prilocaine injection, and return to normal range again after 8-24 hours in most cases [7, 11]. A positive correlation has been shown between the prilocaine dose used for a nerve block, and the time until the maximum met-Hb peak was reached [11,12]. Following a single dose of 300-600 mg prilocaine, met-Hb concentrations in the range of 15% can be detected. This is normally considered harmless, but in certain circumstances, for example in anaemic patients or in

patients with compromised cardiopulmonary function high levels of met-Hb can become clinically relevant [13].

In almost all clinical and laboratory trials, an enormous variation of met-Hb formation has been described. However, little is known about the underlying causes for the high inter-individual variation of methaemoglobinaemia after the administration of prilocaine.

Thus, the purpose of this study was to identify factors that are associated with increased formation of met-Hb levels and to elucidate groups of patients that might have an increased risk.

PATIENTS AND METHODS

Patients of this prospective observational analysis were scheduled for major knee surgery. Following approval of the local ethics review board and written informed consent, patients were randomised to receive a femoral nerve catheter, a lumbar plexus catheter (psoas compartment catheter) or a combination of femoral and sciatic nerve catheters. This randomization was primarily performed to study the analgesic efficacy, the onset time of sensory block and the functional recovery in two distinct studies. Patients younger than 18 years old, patients with a haemoglobin level lower than 120 $g°l^{-1}$, known contraindications for the use of prilocaine (allergies against the drug or other amide-based local anaesthetics, Glucose-6-phosphate dehydrogenase deficiency) and those who had contraindications for a regional anaesthesia procedure (infection at the puncture site, bleeding disorders) were not included.

A total of 162 patients of physical status ASA I – III undergoing major knee surgery were investigated. For all patients a stimulating catheter was used ("Arrow StimuCath continuous nerve block set®" with a 17 Gauge Tuohy needle of 9 or 15 cm length and a 19 Gauge catheter, Arrow® Germany). The technique to identify the femoral or sciatic nerve or the lumbar plexus with the stimulating needle was standardised and performed according to institutional practice. The nerve stimulator current was initially set at 1 mA, with 2 Hz and 0.3 ms (Stimuplex HNS 11, Braun Germany). After initial appropriate motor response was noted with the needle the current was progressively reduced to ≤ 0.3 mA. The catheter was then slowly advanced 5 cm beyond the needle tip under continuous electric stimulation. The four anaesthetists performing the nerve blocks were asked to judge the difficulty of catheter positioning on a 4-point Likert scale (very easy, rather easy, rather difficult or very difficult).

All patients received prilocaine to induce the block via the catheter. 74 patients received 20 ml of a 2 % prilocaine solution (400 mg), 62 patients had 30 ml of a 1 % prilocaine solution (300 mg), and 26 had 40 ml of a 1 % prilocaine solution (400 mg) (see table 1 for details). Thereafter and during 48 hours all patients received a continuous infusion of ropivacaine 0.2 % via the nerve catheter.

About 30 minutes after initializing the block, general anaesthesia was induced with propofol, fentanyl, and rocuronium and maintained with desflurane in all patients.

Venous blood samples for measurement of methaemoglobin concentration were taken 180 minutes after completion of the local anaesthetic injection. The whole blood was immediately analyzed for met-Hb using a Radiometer Copenhagen ABL520 blood gas analyzer (Radiometer Copenhagen, 47852 Willich, Germany). Met-Hb was measured by photometric approach by light extinction method. For a blood sample with haemoglobin content between 102 and 151 $g{\cdot}l^{-1}$ the same-day coefficient of variation for met-Hb-measurements determined by repeated measures of a standardised probe was 0.2-0.3% and the between-day coefficient of variation was 0.3-0.4%.

The following data of potential influence on the formation of methaemoglobin were collected:

Sex, age, weight, height and body mass index (BMI), the technique of regional anaesthesia used, the given prilocaine dose and concentration, an inadvertent vascular puncture, bloody or liquid secretion at the catheter insertion site on the first day as surrogate measures of a higher degree of tissue injury and traumatic puncture, duration of catheter positioning, and difficulty of catheter positioning judged by the performing anaesthetist.

STATISTICS

These variables were subjected to a stepwise linear regression analysis using a backward technique. In each step the least significant factor was eliminated if p was greater than 0.05. The quality of the final regression model was judged using the amount of explained variance of the model and by checking if the standardised residuals were normally distributed using a normal quantile plot as a graphical tool and the Shapiro-Wilk-test as a statistical confirmation. The Durbin-Watson statistic (a value between 0 and 4 with an optimum of 2.0), leverage plots [14] as a graphical tool, and the variance inflation factor (VIF) were used as indicators of autocorrelation or collinearity of parameters included in the

model. Interactions between these factors were investigated using graphical tools (interaction profiles plots) offered by the statistical package used for data analysis (JMP 5.1; SAS Institute Inc., Cary, NC, USA 27513).

A power analysis had revealed that 160 patients would provide a power of 99% to detect an increase of R^2 of 0.25 and higher, attributable to 10 or less independent variables using an F-test with a significance level of 0.01.

RESULTS

Table 1 shows the demographic data of the patients. Continuous data are presented as median and 25th and 75th percentiles (in brackets). Additionally, for the parameters that were included in the final regression model (italicised), the range of values is also presented in squared brackets. For nominal data, the absolute and relative incidence, and for the parameter of the final regression model the type of coding (e.g. “0” or “1”) is given.

Figure 1

Age (years) [range]	66 (57 – 73) [18 – 87]
Height (cm) Weight (kg) Body mass index (kg·m^{-2})	168 (164 – 172) 82 (73 – 92) 28.6 (25.4 – 31.8)
Gender female (coded as "1") males (coded as "0")	 101 (62%) 61 (38%)
Femoral nerve block with prilocaine 300 mg (1%) with prilocaine 400 mg (2%) Femoral nerve & sciatic nerve block with prilocaine 400 mg (1%) Lumbar plexus (psoas compartment) block with prilocaine 300 mg (1%)	109 (67%) 35 74 26 (16%) 26 27 (17%) 27
Absolute prilocaine dose Prilocaine 300 mg Prilocaine 400 mg *Prilocain concentration:* Prilocaine 1% solution Prilocaine 2% solution	 62 (38%) 100 (62%) 88 (54%) 74 (46%)
relative prilocaine dose (mg·kg^{-1}) [range]	4.43 (3.66 – 5.19) [2.59 – 7.41]
Assessment of difficulty of catheter insertion very easy rather easy difficult very difficult time until successful catheter placement (min)	 54 (33%) 56 (35%) 33 (20%) 19 (12%) 6 (4 – 12)
Complications during or after catheter placement Accidental puncture of a vessel bloody secretion at the puncture site	 8 (5%) 12 (7%)

The amount of formed methaemoglobin three hours after block initialisation with 300 mg or 400 mg prilocaine showed a remarkable inter-individual variation. The mean was 2.7 % with values ranging from 0.9 % up to 15.4 %. Two female patients, aged 18 and 21 years respectively, both having received 20 ml of a 2 % prilocaine solution through a femoral catheter, showed clinical signs of cyanosis, but with no further clinical symptoms or impact on subjective well-being. Met-Hb level in these two patients was 10.8 % and 15.4 %, respectively.

Using a stepwise backward regression technique, we could identify four factors that were significant and independent predictors for increased formation of met-Hb. These factors are listed in table 2.

Parameters with a significant and independent influence on the methaemoglobin level following prilocaine injection for regional anaesthesia (results from the backward stepwise regression analysis).

The beta-coefficients can be used to calculate the predicted met-Hb level for each patient. The scaled beta values are the estimates that would be obtained if all variables were scaled to zero mean and a range of -1 to 1 prior to performing the regression computations. Thus they are not affected by the scale of the variable (e.g. remains constant if age would be used in years instead of decades) and can be more easily compared with respect of effect size.

Figure 2

Table 2: CI: confidence interval

Factor	beta (95% CI)	standard error	p-value	Scaled beta
Intercept	2.06 (0.47/3.65)	0.80		
prilocaine (mg·kg^{-1})	0.53 (0.26/0.80)	0.14	0.0002	1.27
1 % prilocaine solution	- 0.36 (-0.63/ - 0.10)	0.14	0.0078	0.37
male sex	- 0.40 (-0.66/ - 0.14)	0.13	0.0027	- 0.40
age (per decade)	- 0.27 (-0.40/ - 0.14)	0.066	< 0.0001	- 0.94

Using the scaled beta-coefficients as an indicator for effect size, it becomes evident that prilocaine dose (mg·kg^{-1} body weight) (increasing met-Hb formation) and age (decreasing met-Hb formation) are the most important influencing factors. Gender (female sex is associated with increased met-Hb formation) and the concentration of the drug are less important factors. For the latter, a 2 % prilocaine solution is associated with increased met-Hb formation compared to the same total dose of prilocaine in a 1 % solution.

The variables that were removed from the model as insignificant are listed in table 3.

They were sorted as to their step at which the factor was removed and thus this information can be used to judge the relative importance of a parameter even though it was not statistically significant on the 5%-level.

Figure 3

Table 3: Factors that were removed from the final regression model.

Factor	Removed at step	Removed at a p-value* of
absolute prilocaine dose	11	0.17
body mass index (kg·m^{-2})	10	0.18
duration of catheter placement (min)	9	0.24
height (cm)	8	0.52
Intervention (lumar plexus block versus other techniques)	7	0.55
inadvertent puncture of a vessel (yes-no)	6	0.57
liquid secretion at the puncture site (yes-no)	5	0.67
intervention (femoral nerve block versus other techniques)	4	0.71
bloody secretion at the puncture site (yes-no)	3	0.77
difficulty of placing catheters, judged by anaesthetists on a 4-point Likert scale (very easy / easy / difficult / very difficult)	2	0.94
weight (kg)	1	0.99

The step at which the factors were removed during the backward procedure and the p-value at which they were excluded are also listed.

* Please note that p-values must not necessarily decrease in the order the factors are removed from the model, because the regression model is recalculated at each step.

The fit of the model was acceptable. About 36% of the variance of the data is explained by the four factors ($p<0.0001$). The quality of the model was good with respect to some commonly used criteria. The residuals of the model (differences between the predicted and the actual levels of met-Hb) were distributed normally and there was no obvious evidence of autocorrelation or collinearity between the four factors included as significant in the final model (Durbin - Watson-test: 1.99; no evidence of clustering using the leverage plots, and VIF for each of the four parameters between 1.04 and 1.19).

DISCUSSION

Prilocaine is a medium-long-acting local anaesthetic with a fast onset of action, comparable with lidocaine and mepivacaine, but prilocaine has a far lower systemic toxicity on the cardiac and central nervous system [1, 2]. Its large volume of distribution protects to a great extent against systemic toxic reactions even in case of accidental intravasal injection [3, 4]. Several toxicologic studies showed about 50 % lower blood levels of the drug than the other fast-onset and medium-long-acting local anaesthetic agents [5, 6, 7]. However, prilocaine bears the disadvantage of the formation of met-Hb induced by its metabolites o-toluidine and nitrosotoluidine [6, 7, 8, 9, 10].

The mechanism of methaemoglobin formation after prilocaine administration has been thoroughly investigated [5, 6 ,7, 8, 9, 15,16,17,18]. In 1960, Löfgren and Tegner described the synthesis of this new local anaesthetic [19]. It was derived from lidocaine, which was known since 1947. Sadove in 1965 was the first to report a sudden discolouration of the blood in the operation field after the use of prilocaine. Furthermore, he recognised a clear cyanosis in the otherwise healthy patient without any signs of acute cardiac or circulatory problems. The spectroscopic analysis demonstrated a distinct increase of methaemoglobin level [20]. The first spectroscopic examinations were followed by many extensive clinical and experimental studies during the next years.

In 1968, Nolte summarised the results of several investigations using prilocaine in doses of 200-2000 mg and in concentrations between 0.5 % and 3 % [11]. He concluded that there was good evidence for a dose-response relationship in the development of methaemoglobinaemia, with noticeable cyanosis occurring with administration of ≥ 600 mg. In a volunteer study, this author tested different doses of prilocaine in 30 healthy young men and women. A clear dose-response relationship was again detected, but a huge inter-individual variability was observed. In this study even small doses of prilocaine (2 mg·kg^{-1}) led to a small but significant elevation of met-Hb that was more marked after 3-6 mg/kg [11]. Kortgen confirmed this dose-responsiveness again in 2003 [9].

However, there is limited information about the underlying causes for the enormous inter-individual variability of methaemoglobinaemia levels observed after administration of comparable doses of prilocaine for regional anaesthesia.

This high and unpredictable variation of met-Hb formation may be a major reason why clinicians are reluctant to use prilocaine in daily practise even though it is licensed in their country (Prilocaine is licenced for peripheral regional blocks in the following countries: Australia, Belgium, Finland, Germany, Great Britain , Japan, Luxembourg, Netherlands, New Zealand, Sweden, Switzerland, Turkey). Eifert for example noticed a vide variation in met-Hb formation among his patients. Receiving a 700 mg prilocaine bolus injection for axillary plexus blockade, the median met-Hb level was 10.1 %, with a maximum between 16 % and 17 %, but no patient showed clinical signs of toxicity [6]. Nolte observed cyanosis after subcutaneous and intramuscular administration of 600 mg at the thigh in volunteers [11],

whereas other authors (Wagner, Kaiser and Tryba) reported about asymptomatic and acyanotic met-Hb elevations in their patients with the same amount of prilocaine [5, 7, 16].

In our own trial, we also identified the dose per kg bodyweight to be the strongest predictive factor for higher met-Hb levels. Since this variable includes the information of the absolute dose (300 or 400 mg) and weight, both parameters were early removed as insignificant from the model. This, of course, does not mean that they are not important parameters but the predictive power of both single parameters was transferred to the combined variable "dose per kg bodyweight". For each $mg \cdot kg^{-1}$, met-Hb was raised by more than 0.5 %. Such a dose-dependency has been described in numerous investigations [review in [11], [9]].

Another important factor was age. Per decade, the predicted level of met-Hb was reduced by an amount of about 0.3 %. This, however, applies only for adult patients and can not be extrapolated to children or even babies who are much more susceptible to met-Hb formation since babies have easily oxidable haemoglobin F and a haemoglobine-reductase enzyme with a lower activity [21]. This age dependency has not yet been described so far.

Our explanation for this observation is the reduced perfusion of tissues in older patients, and thus a slower prilocaine absorbtion. This is in accordance with the well-known clinical observation that the duration of block is highly dependent on age.

Female sex was also detected as an independent factor associated with the formation of higher levels of met-Hb. Overall, male patients had a 0.4 % lower met-Hb value than female patients.

This result is contradictory to the findings of Nolte [11] and Kortgen [9], who denied a significant sex-dependency on met-Hb formation. However, the impact of gender is mainly due to the lower haemoglobin concentrations of females compared to men rather than a true gender dependent effect.

Furthermore, using a higher concentration of prilocaine (2 % versus 1 %) was found to be another risk factor independently from the absolute dose of the drug administered. The same patient developed a 0.36 % higher met-Hb level if he received a 2 % prilocaine solution instead of a 1 % prilocaine solution, even if the total amount of prilocaine in mg was the same. The underlying mechanism remains unclear and has not yet been described so far.

It was interesting to note that both patients with met-Hb levels above 10 % (10.8 % and 15.4 %) had the four risk factors present. Both were females, aged 18 and 21 years, with 54 and 64 kg of weight (7.4 and 6.3 $mg \cdot kg^{-1}$), receiving 20 ml of a 2 % prilocaine solution through a femoral catheter each. Both developed cyanosis, but with no further clinical symptoms. These examples highlight the fact that even though respecting the recommended maximum bolus dose of 400 mg prilocaine without epinephrine-additive for infiltration anaesthesia, considerable levels of methaemoglobinaemia with clinical signs of cyanosis can occur.

The clinical consequences of methaemoglobinaemia are related to the blood level of met-Hb. Methaemoglobinaemia refers to the presence of greater than the normal physiological concentration of 1-2 % methaemoglobin in erythrocytes [22]. Because of its dark blue colour, clinical cyanosis becomes apparent at a concentration of about 15 % [22]. Clinical signs of cyanosis accompanied by a lack of responsiveness to 100 % oxygen are highly suspicious to the presence of methaemoglobinaemia. According to Coleman, clinical symptoms like dyspnoea, nausea and tachycardia in otherwise healthy patients only occur at met-Hb levels exceeding 30 %, deteriorating consciousness occurs at methaemoglobinaemia of around 55 %, while levels of 70 % are usually fatal [23]. According to some authors a met-Hb-level of < 30 % should not be treated in patients without cardio-pulmonary disease [23, 24].

On the other hand, Bellamy [25] and Knobeloch [26] reported symptoms such as cyanosis, tachycardia and vertigo caused by a considerable lower met-Hb concentration in the range of 10 %, a concentration that occurs quite often with prilocaine doses used for loco-regional anaesthesia.

According to Kreutz, induced toxic met-Hb levels are rare but can be life threatening [27]. We have to take into account that in patients with a severe cardiopulmonary disease or pronounced anaemia even gentle met-Hb values far below the so-called toxic levels may lead to pathophysiological significance [13, 28]. Furthermore, patients with an affinity to develop met-Hb can develop much higher met-Hb values accompanied by severe symptoms with the same doses of prilocaine. Among those are babies with their easily oxidisable haemoglobin F and patients with congenital enzyme deficiencies such as the glucose 6-phosphate dehydrogenase deficiency [11]. But despite these theoretical considerations, Wald-Oboussier reported safe prilocaine

administration (6 mg/kg of a 2 % prilocaine solution) in ten female patients with chronic renal failure requiring haemodialysis and a mean haemoglobin of 8.2 %. Met-Hb levels were within the ranges measured in healthy patients [29]. Tryba confirmed this finding, as he did not encounter side effects with 600 mg prilocaine in patients with renal insufficiency or chronic anaemia. Moreover, he states that no complications were described so far in patients with glucose 6-phosphate dehydrogenase deficiency receiving prilocaine [7].

CONCLUSION

In the light of the literature discussed and the obvious low clinical significance of met-Hb levels up to 30 %, our data provide additional evidence for the safety profile of prilocaine, since the patients who are at an increased risk for high met-Hb-levels (e.g. young women) are not likely to suffer clinical side effects under these circumstances. However, the results from this trial help to understand to a certain degree why there is such a high variability in the extent of methaemoglobinaemia between different individuals.

Despite these advances, the results presented demonstrate that an exact and reliably prediction of met-Hb formation is not possible. This highlights the need for a continuing careful use of prilocaine in patients who might be vulnerable to limited oxygen transport capacity, e.g. patient with pre-existing severe cardiopulmonary disease or pronounced anaemia.

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