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# O-Toluidine in Breath-Non-Invasive Prilocaine Monitoring

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## Abstract

The generation of methaemoglobin is a rare but potential life-threatening side effect in the use of the local anaesthetic prilocaine. It is currently only possible to ensure the diagnosis by means of blood tests. Rapid non-invasive diagnosis is desirable, especially for risk patients.

Using a pig model, we induced methaemoglobinemia via application of dimethyl aminophenol and prilocaine (setup I) or natrium nitrite and prilocaine (setup II). Continuous real time breath gas monitoring was performed by proton transfer reaction-time-of-flight-mass spectrometry (PTR-TOF-MS) for non-invasive determination of volatile organic compounds (VOCs).

O-Toluidine, the main metabolite of prilocaine, could be detected in alveolar breath gas by means of PTR-TOF-MS and was confirmed by NTME-GC-MS (needle trap micro-extraction gas chromatography-mass spectrometry). The administration of prilocaine intravenously was clearly reflected with a time lag of a few min by the detection of O-Toluidine in the respiratory gas.

If reliable correlations between prilocaine and methaemoglobin concentrations in blood and O-Toluidine levels in breath can be established, detection of prilocaine induced methaemoglobinemia and prevention of prilocaine poisoning with potentially life threatening hypoxia might be possible by means of non-invasive O-Toluidine analysis in breath.

**Keywords:** Drug-monitoring; Methaemoglobinemia; O-Toluidine; Prilocaine; PTR-TOF-MS; Clinical toxicology

## Introduction

Regional anaesthesia is increasingly used in patients undergoing surgery or painful diagnostic procedures. Maximum doses of local anaesthetics have to be respected in order to minimize toxic side effects which occasionally occur due to accidental intravascular injection, over dosage or unexpected rapid resorption [1]. Recommended doses, unfortunately, do not consider patients' age, body weight, comorbidities and medications. Special haematological side effects of local anaesthetics such as generation of methaemoglobin are rare but can potentially be life-threatening. Methaemoglobinemia has been described for different local anaesthetics [2-4], e.g. prilocaine [5-7]. Children are most frequently affected, less commonly patients with pre-existing glucose-6-phosphate dehydrogenase deficiency, haemoglobinopathies or under accompanying medication favouring methaemoglobinemia. Numerous case reports on emergency treatments of patients with methaemoglobinemia correlated symptoms, such as altered mental and neurological status, hemodynamic problems, cyanosis, exist in the literature. Fast and reliable diagnosis, as non-invasive as possible, is desirable to initiate the appropriate therapy.

## Materials and Methods

After approval by the Local Animal Ethics Committee (LALLF 7221.3-1-007/15; date of permission 31 March of 2015) an animal model was developed to evaluate a new multi wave sensor for reliable detection of hypoxia and dyshemoglobins [8].

Four female German Landrace pigs were investigated with a mean body weight of 42 ± 7 kg. After induction with propofol, fentanyl and cis-atracurium pigs were intubated and mechanically ventilated. Anaesthesia was maintained through continuous infusion of 6-8 mg/kg/h propofol and 0.05-0.1 µg/kg/h fentanyl. An arterial cannula was inserted into the femoral artery for invasive blood pressure measurement and blood gas analysis.

Relevant methaemoglobinemia (target MetHb 10-20-30%) was generated through intravenous application of dimethyl aminophenol (4-DMAP) and prilocaine 1% (setup I) or sodium nitrite ($NaNO_2$) and prilocaine 1% (setup II). While two included pigs A and B of setup I received 2 bolus injections of 100 mg prilocaine, in setup II, pig C received 200 mg of prilocaine via continuous infusion over 10 min. Pig D received 2 bolus injections of prilocaine as in setup I.

Continuous real time breath gas monitoring for non-invasive determination of Volatile Organic Compounds (VOCs) was performed by Proton Transfer Reaction-Time-of-Flight-Mass Spectrometry (PTR-TOF-MS). Lab based Needle Trap Micro-Extraction Gas Chromatography Mass Spectrometry (NTME-GC-MS) at certain time points was applied to confirm marker identities. Details of analytical

methods and instrumentation have been described before [9,10]. Briefly, breath gas for PTR analysis was continuously drawn from the alveolar tube in side stream mode (20 ml/min) by means of a t-piece. O-Toluidine concentrations were quantified in alveolar breath by using a custom-made algorithm. Substance identification from the PTR measurement (m/z) was confirmed by comparing the retention times and mass spectra with those of reference substances using GC-MS.

## Results

O-Toluidine, the main metabolite of prilocaine, could be detected in alveolar breath gas by means of PTR-TOF-MS and was confirmed by NTME-GC-MS. For PTR-TOF-MS analysis of O-Toluidine, linear range was 1-100 ppbV (R2=0.99), detection limit 0.09 ppbV; quantitation limit was 0.23 ppbV. The O-Toluidine concentrations determined in pigs' breath by means of PTR-TOF-MS were in the range of 0-23,5 ppbV. PTR-TOF-MS enabled continuous determination of O-Toluidine in breath gas after intravenous administration of prilocaine. Maximum O-Toluidine concentrations were reached in breath within a few min after (bolus) injection. Repetitive injections of prilocaine induced consecutive increases in breath O-Toluidine concentrations.

The time course of breath O-Toluidine concentrations, starting 10 min before and ending 2-4 h after application of prilocaine is shown in Figure 1 for all four pigs. Maximum breath concentrations of O-Toluidine were approx. two times higher in pigs A and B than in pigs C and D. Continuous application of prilocaine over a period of 10 min in pig C resulted in a longer lasting concentration increase without a traceable first peak.

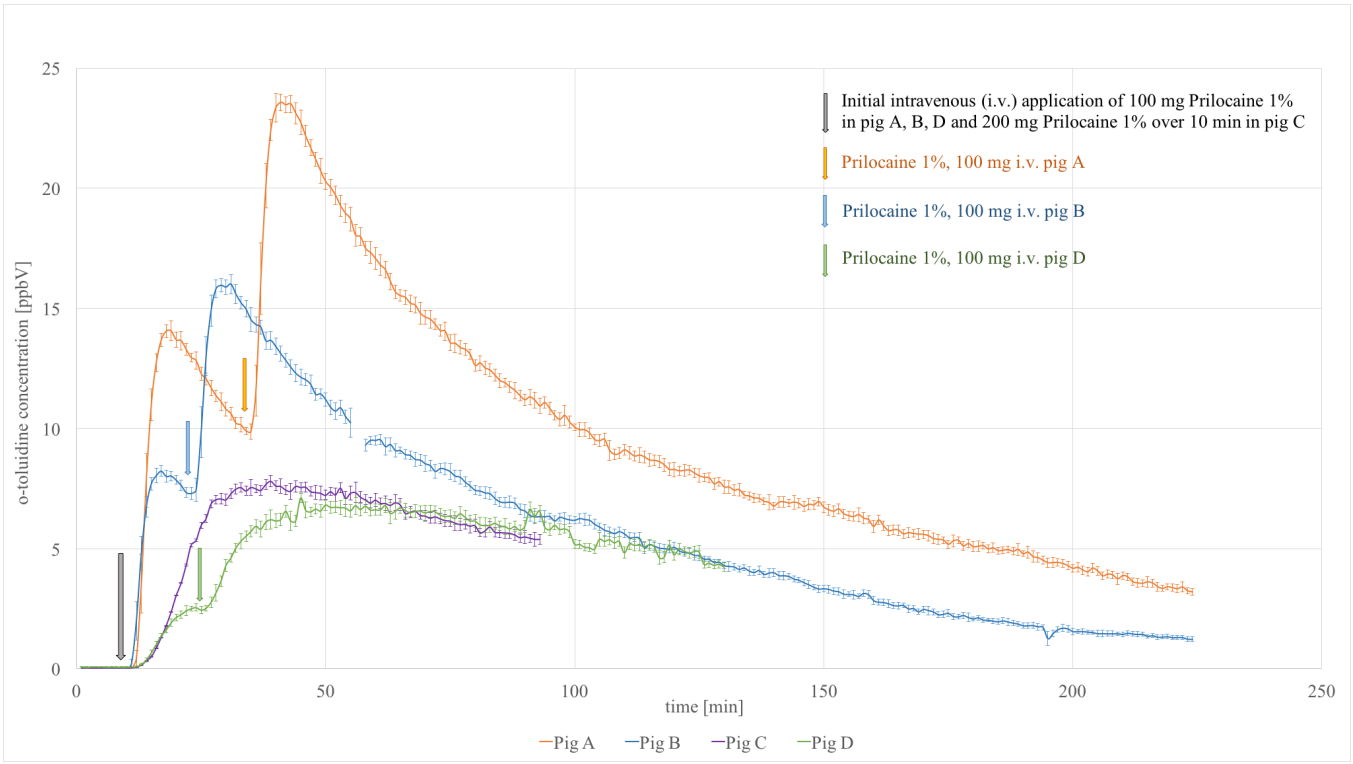


**Figure 1:** Time course of breath O-Toluidine concentrations measured by PTR-TOF-MS. The initial bolus application of 100 mg prilocaine 1% in pig A, B, D and 200 mg prilocaine 1% over 10 min in pig C is marked by black arrow, the additional doses of prilocaine are indicated by coloured arrows for pig A, B, D.

## Discussion

O-Toluidine as the main metabolite of the local anaesthetic prilocaine could be determined in exhaled breath of mechanically ventilated pigs by means of NTME-GC-MS and was continuously monitored in real time by means of PTR-MS. Although blood concentrations of O-Toluidine or prilocaine were not determined a relation of prilocaine concentrations in blood and O-Toluidine in breath gas seems evident. The different pharmacokinetic behaviour of prilocaine in pigs A and B versus pigs C and D can be explained by the co-medication used for induction of methaemoglobinemia. Whereas 4-DMAP had little effect on haemodynamic, $NaNO_2$ triggered a pronounced vasodilatation with consecutive hypotension.

If reliable correlations between prilocaine and methaemoglobin concentrations in blood and O-Toluidine levels in breath can be established, detection of prilocaine induced methaemoglobinemia and prevention of prilocaine poisoning with potentially life threatening hypoxia might be possible by means of non-invasive O-Toluidine analysis in breath.

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## Conflict of Interest

All authors declare that conflicts of interest do not exist.

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