



**Karolinska
Institutet**

**Institutionen för Fysiologi och Farmakologi
Sektionen för Anestesiologi och Intensivvård**

Genetic and cognitive aspects on recovery after propofol anaesthesia

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid
Karolinska Institutet offentligen försvaras i Nanna Svartz
Auditorium, Karolinska Universitetssjukhuset, Solna

Fredagen den 13 februari 2015 kl 09.00

av

Marja Lindqvist

Leg. läkare

Huvudhandledare:

Professor Jan Jakobsson
Karolinska Institutet
Institutionen för Klinisk Vetenskap
Anestesi och Intensivvårdskliniken
Danderyds sjukhus

Bihandledare:

Medicine doktor Håkan Björne
Karolinska Institutet
Institutionen för Fysiologi och Farmakologi
Sektionen för Anestesiologi och Intensivvård

Fakultetsopponent:

Professor Jonas Åkesson
Lunds Universitet
Institutionen för Anestesiologi och
Intensivvård

Betygsnämnd:

Professor Ulrika Nilsson
Örebro Universitet
Institutionen för Hälsovetenskap och Medicin

Professor Rolf Sandin
Karolinska Institutet
Institutionen för Fysiologi och Farmakologi
Sektionen för Anestesiologi och Intensivvård

Docent Carl-Olav Stiller
Karolinska Institutet
Institutionen för medicin
Enheten för klinisk farmakologi

Stockholm 2015

ABSTRACT

Propofol is one of the most used intravenous anaesthetics in the western world. It is often used for ambulatory surgery due to favourable pharmacokinetic properties allowing quick onset and short emergence time. However, there is considerable inter-individual variation in pharmacokinetics and dynamics as well as gender differences. Differences in metabolism due to polymorphic enzymes may be a contributing factor to this variation. To enable early and smooth discharge from hospital after ambulatory surgery, a quick postoperative cognitive recovery is essential. It is not known whether the great variation in propofol pharmacokinetics and pharmacodynamics affect the cognitive recovery of the ambulatory patient receiving propofol.

By studying correlation between genotype and propofol metabolite production both in liver microsomes and in humans after propofol anaesthesia, we aimed to further describe the variations in propofol pharmacokinetics. Postoperative cognitive recovery in women undergoing ambulatory breast cancer surgery with propofol or desflurane anaesthesia was studied, using the PQRS and CFQ as assessment tools. Further the cognitive performance according to PQRS in a test re-test situation in pre-surgery cancer patients compared to controls was evaluated.

Our results demonstrate a great variation in production of propofol metabolites in vitro and in vivo, but no correlation between metabolite level and genotype. Females showed a higher propofol metabolite level compared to men after both bolus dose and infusion of propofol. Cognitive recovery was similar after propofol and desflurane anaesthesia, and subjectively not complete one week after surgery. We found that pre-surgery cancer patients expressed a higher level of anxiety and had lower cognitive baseline test performance compared to controls, resulting in a high exclusion rate in the patient group. The groups had a similar re-test performance in the PQRS cognitive domain.

In conclusion, we found a considerable variability in production of propofol metabolites but no correlation to genotype. There was an increased production of propofol metabolites in women compared to men. The protracted postoperative cognitive recovery assessed by PQRS and CFQ after ambulatory surgery was similar after propofol and desflurane anaesthesia, suggesting possible remains of propofol or its metabolites do not affect cognitive performance more than residual effects of desflurane. When assessing postoperative cognitive recovery it should be acknowledged that the anxiety and stress caused by a severe disease and wait for surgery may have an impact on cognitive PQRS test performance. The use of the revised PQRS cognitive scoring system may lead to the exclusion of a considerable part of the patients due to too low baseline performance.

Key words; propofol, CYP2B6, UGT1A9, propofol metabolites, gender difference, postoperative cognitive recovery, desflurane, Postoperative Quality of Recovery Scale, Cognitive Failure Questionnaire