volume was made up to 5 ml using the sodium sulphate solutions of various concentrations. The resulting dispersions were mixed and the absorbances were measured within 5 min at 400 nm on a Shimadzu 1601 UV-Visible Spectrophotometer against respective blank.

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Onset and offset pharmacodynamics of propofol

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Propofol whole blood and plasma concentrations at offset of hypnosis in eighteen patients were inversely related to patient age and body fat. The relationship between propofol concentrations and body fat is derived from the relationship between age and body fat and age was the single independent predictor of concentrations at offset of propofol hypnosis.

Patient age and body fat may influence propofol pharmacodynamics. Concentrations at which 50% of volunteers fell asleep following a 2 mg/kg bolus dose were higher in younger than in elderly subjects (Schnider et al. 1999) and lower hypnotic doses, shorter times to hypnosis and higher propofol plasma concentrations were also noted as patients aged (Adachi et al. 2001). Total body weight also influenced propofol pharmacodynamics, after adjustment of propofol infusion rate to patient body weight. Heavier patients needed higher infusion doses and displayed shorter times to hypnosis than lighter patients (Adachi et al. 2001) and propofol doses were inversely related to lean body mass and not body weight (Adachi et al. 2001; Servin et al. 1993; Leslie and Crankshaw 1991; Chassard et al. 1999). Obese patients were at risk of overdose when weight-normalised propofol infusions were used (Gepts et al. 1987). The current study specifically examined the influence of patient age and body fat on propofol whole blood and plasma propofol concentrations at onset and recovery.

As age increased there was a significant decrease in propofol whole blood and plasma offset concentrations (Fig.). At onset no such relationship was observed between age and propofol concentrations in either whole blood or plasma. When patients were divided into two age groups ($<$ or $>$65 years), similar to the age cut-off used previously (Adachi et al. 2001), patients over 65 years required lower whole blood propofol concentrations (4.1 ± 1.7 μg/mL) at onset compared to patients less than 65 years of age (5.3 ± 1.3 μg/mL, $P < 0.05$). Similarly, patients over 65 years recovered from propofol at lower concentrations (1.3 ± 0.4 μg/mL) compared to patients under 65 years (2.3 ± 0.9 μg/mL, $P < 0.01$). An inverse correlation was noted between body fat and propofol whole blood (or plasma) onset ($r^2 = 0.382$, $P < 0.01$) and offset ($r^2 = 0.353$, $P < 0.05$) concentrations; as body fat increased whole blood and plasma concentrations at onset and offset decreased. Hypothesising that body fat increases with age, indeed it was found that body fat correlated positively

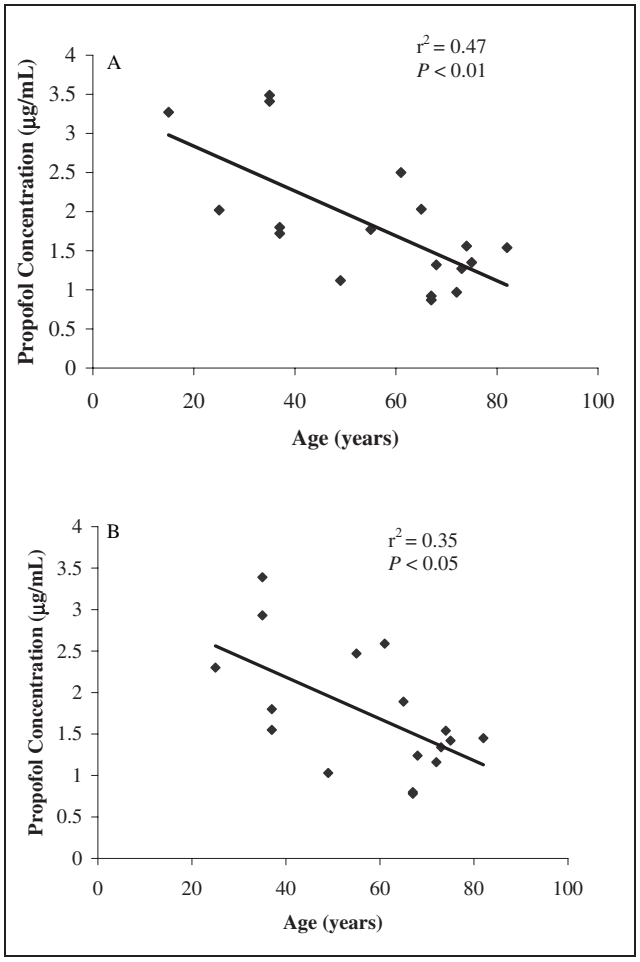

Fig.: Propofol whole blood (A) and plasma (B) offset concentrations and age

with age ($r^2 = 0.58$, $P < 0.01$). Multiple linear regression also identified age and body fat as affecting propofol offset concentrations. However, stepwise multiple regression identified only age as the single independent predictor of propofol offset concentrations in either plasma (offset conc = 3.278–0.02664 age, $r^2 = 0.486$, $P = 0.006$) or whole blood (offset conc = 3.410–0.0287 age, $r^2 = 0.465$, $P = 0.002$).

Elderly patients were more sensitive to propofol as previously reported (Schnider et al. 1999, Adachi et al. 2001). A significant correlation also existed between body fat and propofol pharmacodynamics, supporting a lean body mass correction (Gepts et al. 1987) for predicting propofol doses. Influence of body fat on propofol pharmacodynamics was due to the co-existing relationship between age and propofol pharmacodynamics. The relationship between propofol concentrations and body fat is derived from the relationship between age and body fat. Age appears to be the major determinant of propofol pharmacodynamics. These results differ somewhat from a recent finding that age and body fat are independent predictors of propofol pharmacodynamics (Kazama et al. 2003).

Experimental

1. Patients and propofol dosing

After ethics approval eighteen patients (9 M/9 F, 15–82 yrs, 50–105 kg, 8–50% body fat) undergoing urological or gynaecological surgery were studied; benzodiazepines/high doses of opioids were not used. Lean body mass (LBM) was assessed using Lipo-Trak® (Bodystat, Douglas, Isle of Man), based on bioelectrical impedance measurement. A current (I) generated a voltage (V) between two points on the body and impedance (V/I ratio) was estimated. LBM (or body fat) was then calculated using Lipo-Trak®® software based on Deurenberg's equation (Deurenberg et al. 1991) using impedance measurement and anthropometric variables such as age, body height, body weight and gender. Propofol was administered as a target-controlled infusion (Kenny 1997); the target was 2 μg/mL which was increased to 4 or 6 μg/mL if required. Patients were asked to open their eyes every ten seconds, lack of response to this command was taken as onset of hypnosis. Upon discontinuation of propofol infusion, offset (loss of hypnosis) was determined by response to the same verbal command.

2. Blood sampling, propofol assay and statistical analysis

Two venous blood samples, one at onset and one at offset of hypnosis were taken from each patient. Propofol in both plasma and blood was determined since the blood to plasma ratio is not unity. Liquid chromatography with fluorescence detection was used (Yeganeh and Ramzan 1997), calibration curves ranged from 1.8 to 9.1 μg/mL, inter- and intra-day variability was 3 to 8% and the limit of quantification was 0.45 μg/mL. Influence of patient variables were evaluated using univariate and multiple linear regression; $P < 0.05$ was considered significant.

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