INTRODUCTION: Alterations in the metabolism of cytochrome P450 and uridine glucuronosyltransferase substrates were demonstrated in a murine model of sickle cell anemia (SCA) (1). In children with SCA, the pharmacokinetics (PK) of morphine exhibited large inter-individual variability, suggesting that considerable individualization of morphine dosing is necessary (2). Although the PK of propofol have been widely studied, we were unable to find any study in children with SCA. We aimed to assess the PK of a bolus of propofol in children with SCA undergoing elective surgery.

METHODS: REB approval and parental consent were obtained to study 16 children with SCA. Propofol 3.0 mg/kg i.v. was administered and venous blood was sampled. Samples were prepared by solid-phase extraction, and analyzed by HPLC with fluorescence detection. We assessed the PK of propofol using a model that included a central compartment interacting with 3 peripheral compartments, one of which acted as a closed circuit with no drug elimination. The other 2 peripheral compartments irreversibly eliminated the drug, as is expected to occur in liver and lung. The central compartment was also modeled assuming an irreversible lost of propofol (simulating renal clearance). We assumed a combination of slow and fast transfer rates between central and peripheral compartments. Simulations were performed using SAAM II.

RESULTS: Based on physiological plausibility, we explored 2 assumptions: a) a closed circuit was formed between the central and a peripheral compartment and b) this peripheral compartment also drained unidirectionally to the "liver", another peripheral compartment (semi-closed model). As propofol is highly lipophilic, it was assumed that the transfer rate from central to peripheral compartments in the closed circuit was faster than the transfer rate for propofol from this peripheral back to the central compartment. All patients were successfully modeled using the closed-circuit approach and indicators of quality of adjustment were enhanced using this model (Figure).

DISCUSSION: Our data suggest that the PK of propofol in children with SCA are more complex than the classic 3 compartment model, and should include at least one peripheral compartment interacting with the central compartment as a closed circuit. In addition, our analysis supports that irreversible drug elimination occurs from peripheral compartments (e.g. liver and lung), and not only from the central compartment. Further modeling of the predictability of this model is desirable.