Title: Pharmacokinetics of Antibody-Drug Conjugates: TMDD Equations, Approximations, and Identifiability of Model Parameters.

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Objectives: To derive equations that describe distribution, deconjugation, elimination and interaction with the target of antibody-drug conjugates (ADC); to derive a Michaelis-Menten approximation of these equations; to investigate identifiability of model parameters given typically available measurements and clinically feasible sampling schemes.

Methods: Concentration-time equations were derived for the ADC - target system that includes the naked antibody, ADCs with various loads, free drug, free target, and various antibody ADC-target complexes. It was assumed that the antibody PK and target properties do not depend on the drug load except of the non-specific clearance and deconjugation rate parameters. The Michaelis-Menten approximation of these equations was derived based on the assumption of fast internalization of the ADC-target complex. Identifiability of model parameters was investigated using an optimal design software. The parsimonious model, flexible enough to describe the typically available measurements yet simple enough to be identifiable was suggested. Various generalizations of the proposed model were discussed.

Results: The ADC system can be described using the general TMDD framework with an additional element that accounts for the deconjugation process. Given the typically available measurements, parameters of the individual ADC species (ADCs with specific drug loads) are not identifiable. Assumptions that relate ADC non-specific clearance with the drug load are required. In particular, the system where clearance does not depend on the drug load is identifiable. The system where clearance linearly depends on the drug load also can be identifiable. Similarly, deconjugation rate of individual ADC species can be identifiable only under specific assumptions on how deconjugation rate depends on the drug load; the individual ADC deconjugation rates cannot be estimated from the typically available data. The system where deconjugation rate linearly depends on the drug load can be identifiable.

Conclusions: The Michaelis-Menten approximation of the TMDD model can be used to describe the interaction of ADC with the target when internalization rate is fast. Assumptions that describe dependence of the ADC parameters on the drug load are necessary to make the system identifiable. In particular, the system with ADC parameters linearly dependent on the drug load can be identifiable.