Can we predict saliva penetration of drugs?: a systematic review

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Introduction. Saliva is an emerging matrix for therapeutic drug monitoring (TDM).

Aims. To determine the physicochemical properties that influence the penetration of drugs from plasma to saliva.

Methods. Medline and Web of Science (1980−2023) were searched for human clinical studies, which determined drug pharmacokinetics in both saliva and blood. Studies with at least 10 subjects and 5 paired saliva-blood concentrations per subject were included. For each study, the ratio of the area under the concentration–time curve between saliva and total (protein-bound + unbound) blood was determined to assess penetration into saliva. Physicochemical properties of each drug (pKa, lipophilicity, molecular weight, physiological charge, hydrogen-bond donor–HBD, hydrogen-bond acceptor, polar surface area–PSA, rotatable bonds–ROB, fraction of drug unbound to plasma protein) were obtained from PubChem and Drugbank. Drugs were categorised by their ionisability and saliva-to-blood ratios were predicted with adjustment for protein binding and physiological pH via the Henderson-Hassenbach equation. Spearman correlation analyses were performed for each category to identify factors predicting saliva penetration (α=5%). Study quality was assessed by the Risk Of Bias In Non-randomised Studies–of Interventions (ROBINS-I) tool.

Results. Overall, 48 studies including 44 drugs (antipsychotics, antimicrobials, immunosuppressants, antithrombotic, anticancer, and cardiac drugs) were included. The median saliva-to-blood ratios were similar for drugs in the amphoteric, basic, and acidic groups (0.59, 0.50 and 0.43, respectively) and lowest for drugs in the neutral group (0.16). Higher penetration into the saliva of acidic group drugs was associated with lower ionisation and protein binding (predicted vs. observed ratios: r^2=0.85, P=0.009, n=6). For basic group (n=22), pKa was the only predictor (P=0.02). For amphoteric group (n=10), HBD and PSA were predictors (P<0.05). For neutral group (n=6), HBD and ROB were predictors (both P=0.05). All the studies had a low-to-moderate risk of bias.

Discussion. Many commonly used drugs penetrate saliva. Physicochemical properties can partly predict saliva penetration. Further research is required to evaluate the contribution of drug transporters and physiological factors influencing saliva penetration of drugs.