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Perspective on the Use of Limited Sampling Strategies to Assess Drug Exposure in the Era of Microsampling

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1 **Perspective on the Use of Limited Sampling Strategies to Assess Drug**
2 **Exposure in the Era of Microsampling**

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4 Letter to the Editor

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17 The field of microsampling in therapeutic drug monitoring (TDM) has been revived recently
18 with the emergence of second-generation microsampling devices. To date, these approaches
19 have relied on absorptive papers for blood collection; however, the use of these devices is
20 burdened by numerous shortcomings, related to volume collection and patient hematocrit,
21 which can induce bias in drug quantification. The emergence of devices such as volumetric
22 absorptive microsampling (VAMS) limits analytical issues and offers new opportunities for
23 widespread application of microsampling for TDM (1). Herein, the main aspect is the potential
24 for determining the area under the curve (AUC) of drug concentrations. AUC is the ideal
25 pharmacokinetic index for evaluating drug exposure; however, determining AUC requires
26 collection of multiple blood samples over the drug administration interval, usually through
27 venipuncture—an invasive procedure. Further, it requires trained staff and is a time-consuming
28 procedure. Consequently, TDM based on AUC was restricted to specific therapeutic situations.
29 Therefore, pharmacologists have developed population pharmacokinetic modeling (PPM)
30 approaches and limited sampling strategies (LSSs) to estimate AUC from a limited number of
31 blood samples (2). PPM allows the estimation of individual patient pharmacokinetic
32 parameters; this enables prediction of drug concentration over time and subsequently, global
33 exposure to the drug (i.e., the AUC) in a specific patient. It is then possible to identify the time-
34 points carrying the highest information weight in the model and determine the lowest number
35 of blood samples needed to predict the AUC with the highest degree of confidence. However,
36 although PPM approaches coupled with LSSs decrease the uncertainty in estimating AUC, they
37 do not completely abolish it. Therefore, predictions are given with a confidence interval because
38 of the associated residual, non-reducible error (3). LSSs with 1 to 4 time-points for blood
39 collection have been developed for various drugs, thus decreasing the burden of invasiveness
40 for patients. This approach has been widely used for TDM of drugs, such as
41 immunosuppressive, anticancer, and anti-infective drugs. LSSs are aimed at minimizing the

42 invasiveness of iterative venipuncture. However, this invasiveness is largely reduced by
43 microsampling procedures. Moreover, LSS could be combined with microsampling using
44 VAMS to determine AUC in patients. However, owing to the minimally invasive nature of
45 microsampling, obtaining the complete “real” AUC (with at least 8-10 sample points) using this
46 new approach may have virtues over the “estimated” AUC with LSS and PPM (with 4 sample
47 time-points or less).

48 First, the interest of LSS instead of microsampling to estimate complete AUCs must be assessed
49 on a case-by-case basis, depending on the mean predictive error, which when low (<10%), may
50 favor substitution of the complete AUC for LSS. However, such evaluations should be
51 conducted on an external set of data with enough patients because, despite a low mean error,
52 AUC can be poorly estimated in specific patients. For example, a study (4) reported a -7.9%
53 mean prediction error for levofloxacin AUCs using LSS in an external validation set; however,
54 the AUC was underestimated by >15% and >30% for 3 patients and 2 patients, respectively,
55 out of 20 patients. This raises concerns about the loss of performance of the approach, although
56 it may affect a limited number of patients.

57 Second, a LSS is only applicable to the patient population in whom the model has been built.
58 There are several examples of the mishandling of modeling estimation in inappropriate
59 populations. For example, Perinel et al. used a model developed in patients with rheumatoid
60 arthritis treated with hydroxychloroquine to simulate various dosing regimens of a drug for
61 critically ill patients with severe acute respiratory syndrome coronavirus 2 infection (5). As
62 expected, the simulated and observed data were completely discordant, showing the
63 dependency of a modeling approach on the patient population used to develop it. Determination
64 of complete pharmacokinetic profiles using microsampling strategies instead of limiting
65 observations to a limited number of time-points avoids similar pitfalls and enables calculation
66 of a more accurate AUC. It is relevant for every individual, especially those with atypical

67 pharmacokinetics, and is appropriate in every type of patient population. Further, it is equally
68 efficient and suitable for patients with limited venous access, such as elderly patients or
69 neonates. However, performing 8 to 10 time-point concentration measurements rather than
70 using a 1- to 4-sample LSS can increase the overall cost of analysis. Another advantage of LSSs
71 is the reduction in hospital stay duration because only a few samples have to be collected during
72 the first post-intake hours compared to that required for determining complete pharmacokinetic
73 profiles. These benefits must be balanced with the therapeutic benefits of accurately evaluating
74 drug exposure owing to a complete pharmacokinetic profile. Herein, a major asset of
75 microsampling is its ability to be used at home by patients after appropriate training (6); up to
76 10 samples could be collected within a day without the need for hospitalization.

77 Nevertheless, with VAMS, dried whole blood is collected, and plasma samples are not
78 available; further, target therapeutic ranges of most drugs have been determined in plasma, and
79 interchangeability has not been evaluated. Hence, the first step in implementing microsampling
80 for TDM is to validate the agreement between plasma and capillary-dried whole blood drug
81 measurements. In some cases, a factor must be applied to derive the plasma concentration from
82 whole blood concentration, depending on the drug distribution in red blood cells (6). For drugs,
83 such as immunosuppressive drugs, whose concentrations are usually measured in whole blood,
84 microsampling approaches are perfectly suitable (7). For newly approved drugs, wherein
85 therapeutic ranges remain to be determined, conducting a data-rich pharmacokinetic analysis
86 using a microsampling strategy from the start of a TDM program offers a unique opportunity
87 to decipher drug exposure-effect relationships.

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