Phase I *in vitro* and *in vivo* metabolism of the designer opioid furanylfentanyl

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**Introduction**

Lately, designer opioids (DO) have gained more relevance on the market of new psychoactive substances (NPS). One predominant subgroup of DO are fentanyl derivatives. These compounds pose a particularly high risk to human health because many of these substances are several-fold more potent than morphine. In the present study the *in vitro* phase I metabolism of furanylfentanyl (Fu-F) was investigated using pooled human liver microsomes (pHLM). The results were compared to the *in vivo* phase I metabolites detected in an authentic urine sample to identify the most suitable targets for urine analysis.

**Methods**

**pHLM assay – *in vitro* phase I metabolism**

**Preparation of urine samples – *in vivo* metabolism**

**Results & Discussion**

In total, 15 *in vivo* phase I metabolites were identified. 4-Anilino-N-phenetylpyridine (4-ANPP, M14), formed by amide hydrolysis, was the most dominant metabolite detected. Additionally, subsequent biotransformations of 4-ANPP (hydroxylation, methylation, formation of dihydridiols) and N-des-alkylation of Fu-F leading to nor-furanylfentanyl (M05) were observed as primary metabolic reactions (Fig. 1). Most of these metabolites could be detected in the *in vitro* assay as well. However, the phase I metabolic profile and the ratios of metabolites showed significant differences in vivo and *in vitro* (all tentatively identified metabolites in *vivo* are shown in ranked order in Fig. 3).

Recently published studies on the metabolism of Fu-F nominate the dihydrido metabolite of the intact Fu-F (M16) as an additional main metabolite (10). This particular metabolite was not present in this case. Most of the metabolites detected in the urine sample originated from further biotransformations of the amide hydrolysis product (M14).

**Conclusion**

The pHLM assay is a quick and straightforward tool to predict main phase I *in vivo* metabolites of the fentanyl derivatives. As described for other DO before the parent compound Fu-F can be targeted for detection of drug use in urine samples. In addition the postulated main metabolites may serve as additional urinary biomarkers for Fu-F consumption and might provide longer detection windows.

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**References**


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