Compliance testing in methadone substitution therapy: evaluation of CEDIA EDDP taking account of methadone dose, urinary pH, creatinine and CEDIA Sample Check

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AIMS: Methadone maintenance therapy has to ensure that patients use the supplied methadone as prescribed and that patients are not taking additional illicit drugs. To verify compliance to this, random urine drug testing is commonly performed with immunoassay. The laboratory has to be able to detect different kinds of non-compliance in urine drug testing. The aim of this work was to evaluate EDDP for this purpose taking account of dose, urinary pH, creatinine and CEDIA Sample Check.

METHODS: During a 5 month period 6985 fresh routine urine samples from 5 different out-patient clinics (OP-A to E) in Berlin were analysed semiquantitatively with CEDIA reagents for EDDP (cutoff 100ng/mL), methadone (OP-A only), Sample Check and for pH (DRI) and creatinine (DRI). Instruments used were a Hitachi 911 or Olympus AU640. Only patients on methadone or l-methadone with known dose were included. Number of patients/samples: OP-A: 218/2908, OP-B: 178/2037, OP-C: 81/450, OP-D: 110/529, OP-E: 234/1061. Methadone dosing range was 3-300mg/d. methadone-positive/EDDP-negative samples were further investigated with HPLC-DAD (LOQs: 10ng/mL, linearity: 10-2000ng/mL). Samples were defined as spiked when they contained >10000ng/mL methadone and <100ng/mL EDDP.

RESULTS: *1. pH:* Mean value of urinary pH was 6.1 (median 6.0) but distribution was bimodal with a maximum at pH 5.2 and a minor maximum around pH 7.0. Surprisingly, 18% of the samples were ≥ pH 7.0. Fourty-one samples from OP-A were below the 300ng/mL methadone cutoff but were clearly positive for EDDP and 88% of these had an pH ≥7. Two samples were suspected of being adulterated (pH 10.8 and 3.7).

2. Creatinine: Mean creatinine level was 146mg/dL (median 131) with 0.34% <5mg/dL, 2.6% <20mg/dL and 23.4% >200mg/dL. In comparison random data from clinical chemistry department (>2000 patients, 3003 samples) revealed a different distribution: mean 102mg/dL, median 83mg/dL, 0.1% <5mg/dL, 1% <20mg/dL and only 8% >200mg/dL.

3. Sample Check: 94% of all samples were in the 85-105% range of maximum enzyme activity of the CEDIA Sample Check. Only 0.29% were >105%, which proved to be related to urinary tract infection and led to false positive results with CEDIA in some cases. The fraction of samples below 85% enzyme activity was 5.9%. Interestingly, 19% of the samples within the CEDIA EDDP measuring range had reduced enzyme activity. Surprisingly, creatinine values for this group of samples were much higher (mean 272mg/dL, median 262mg/dL) than for all samples. Reanalysis of these samples after dilution gave EDDP values over the measuring range. It could be shown for all samples, that there was a correlation between high creatinine values and reduced CEDIA enzyme activity. Considering this, only one sample with a Sample Check value

of 61% was classified adulterated. 4. EDDP: no false negative sample was observed due to pH, low dose, low creatinine or reduced enzyme activity. Most samples (84.3%) were over the CEDIA EDDP measuring range (>2000ng/mL). Methadone spiked samples were found in the following proportions (number of samples/patients): OP-A: 22/21(9.6%), OP-B: 46/37(20.8%), OP-C: 24/11(13.6%), OP-D: 12/11(10%) and OP-E: 42/34(14.5%).

CONCLUSIONS: Adulteration of samples seemed to be rare in the investigated population. However, urinary pH and creatinine tended to higher values when compared to the "normal population". Increased pH led to clinically false negative methadone values, while EDDP excretion was not influenced. Highly concentrated urines often showed paradoxically lowered CEDIA EDDP values due to reduced enzyme activity even at high doses but no false negatives had been observed. Testing for EDDP instead of methadone revealed 10-20% of the patients as "spikers". EDDP as target analyte is preferred over methadone in compliance testing. However low semiquantitative data should be looked at in the context of dose, Sample Check and creatinine.

KEYWORDS: *EDDP, Methadone, Sample Check, Compliance*

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